Functional Residual Capacity

Development of new monitoring techniques
for critically ill patients

Cecilia Olegård

UNIVERSITY OF GOTHENBURG

Department of Anaesthesiology and Intensive Care
Institute of Clinical Sciences at Sahlgrenska Academy
University of Gothenburg
Gothenburg, Sweden
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Cecilia Olegård

Institute of Surgical Sciences,
Department of Anaesthesiology and Intensive Care.
Sahlgrenska University Hospital, Gothenburg University, Sweden.

Abstract

Functional residual capacity (FRC) and end-expiratory lung volume (EELV) are important parameters for respiratory monitoring in critically ill adult and paediatric patients. Until now we have lacked clinically useful methods to measure these lung volumes. In this thesis two methods for bedside measurements of FRC in mechanically ventilated patients have been developed and evaluated. The first method (FRC_{flux}) is based on quantification of metabolic gas fluxes of O_2 and CO_2 during a short apnoea. The second method is a modified nitrogen wash-out/wash-in technique (FRC_{N2}) based on standard monitoring equipment. The possibility to combine measurements of EELV with a tool to assess lung mechanics by measuring volume dependent compliance (VDC) was also assessed.

***Methods*:** Baseline exchange of oxygen and carbon dioxide was measured using indirect calorimetry for both the FRC_{flux} and the FRC_{N2} method. End-tidal (~alveolar) O_2 and CO_2 concentrations were obtained before and after a few seconds of apnoea, and FRC_{flux} was calculated according to standard wash-out/wash-in formulae taking into account the increased solubility of CO_2 in blood when tension is increased during apnea. The FRC_{N2} was calculated using changes in inspiratory and end-tidal gas concentrations breath-by-breath after a small step-change for inspiratory oxygen (F_IO_2). These methods were validated both in mechanically ventilated patients and in lung models. The FRC_{N2} technique was also tested in small children and infants both perioperatively, using a Mapleson -D system, and in the ICU. A lung injury animal model was used to investigate the effects on FRC_{N2} and VDC by lung lavage and after three different lung recruitment manoeuvres (RMs).

***Results*:** The FRC measurement methods showed good precision and reproducibility. Experimental acute lung injury caused by lung lavage resulted in large decreases in EELV and VDC. There were differences in the response to RMs in individual animals demonstrated by combined measurements of changes in EELV and volume-dependent compliance.

***Conclusions*:** New methods have been developed for measurements of lung volumes using standard monitoring equipment only. The FRC_{N2} method makes it possible to measure lung volumes in realtime at the bedside in combination with volume-dependent compliance. Combined measurements of changes in lung volume and compliance could be helpful to define responders and non-responders to lung recruitment manoeuvres, and to increases in positive end-expiratory pressure (PEEP). These new monitoring tools may help clinicians to tailor ventilation to the individual patient and hopefully attenuate the risk for ventilator induced lung injury.

***Keywords*:** FRC, functional residual capacity, EELV, end expiratory lung volume, volume dependent compliance, VDC, acute respiratory failure, recruitment manouvre, PEEP
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CONTENTS

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals I-IV.

I. Stenqvist O, Olegård C, Söndergaard S, Odenstedt H, Karason K, Lundin S. **Monitoring functional residual capacity (FRC) by quantifying oxygen/carbon dioxide fluxes during a short apnea.** *Acta Anaesthesiol Scand 2002; 46:732-739*

II. Olegård C, Söndergaard S, Houltz E, Lundin S, Stenqvist O. **Estimation of functional residual capacity at the bedside using standard monitoring equipment: A modified nitrogen Wash-out/wash-in technique requiring a small change of the inspired oxygen fraction**. *Anesth Analg 2005; 101:206-12*

III. Olegård C, Söndergaard S, Pålsson J, Lundin S, Stenqvist O. **Validation and clinical feasibility of nitrogen wash-in/wash-out functional residual capacity measurements in children.** *Acta Anaesthesiol Scand 2009; Oct 15 [Epub ahead of print]*

IV. Olegård C, Söndergaard S, Odenstedt H, Lindgren S, Lundin S, Stenqvist O. **Volume-dependent compliance and resistance during three different recruitment maneuvers.** *In manuscript 2010.*

ABBREVIATIONS AND EXPLANATIONS

ALI	acute lung injury
ARDS	acute respiratory distress syndrome
ARF	acute respiratory failure
BV	baseline ventilation
Cfin	compliance at final part of tidal volume
Cini	compliance at initial part of tidal volume
Cmid	compliance at middle part of tidal volume
CO_2	carbon dioxide
CT	computed tomography
$\Delta EtCO_2$	end-tidal CO_2 change
ΔFRC	functional recidual capacity change
EELV	end-expiratory lung volume
F	fraction
$F_{\overline{E}}CO_2$	mixed expiratory fraction of CO_2
$F_{\overline{E}}O_2$	mixed expiratory fraction of O_2
$F_{ET}CO_2$	alveolar/end-tidal fraction of carbon dioxide
$F_{ET}CO_{2post}$	end-tidal carbon dioxide fraction after apnoea
$F_{ET}CO_{2pre}$	end-tidal carbon dioxide fraction before apnoea
$F_{ET}N_2$	end-tidal N_2 fraction
$F_{ET}O_2$	end-tidal O_2 fraction
$F_{ET}O_{2post}$	end-tidal oxygen fraction after apnoea
$F_{ET}O_{2pre}$	end-tidal oxygen fraction before apnoea
F_IN_2	inspiratory N_2 fraction
F_IN_{2end}	inspiratory N_2 fraction at end of washout
F_IN_{2ini}	inspiratory N_2 fraction at start of washout
F_IO_2	the inspiratory fraction of oxygen
FRC	functional residual capacity
FRC_{alv}	alveolar functional recidual capacity
FRC_{flux}	FRC measured by O_2/CO_2 fluxes
FRC_{N2}	FRC measured by nitrogen wash-out/wash-in
He	Helium
I:E	inspiratory to expiratory ratio
ICU	intensive care unit
kPa	kilo Pascal
$LCBCO_2$	carbon dioxide in lung capillary blood caused by apnoea
MBNW	multiple breath nitrogen washout
N_2	nitrogen
O_2	oxygen
P	pressure
P_{alv}	alveolar pressure
PCRM	pressure control recruitment manoeuvre
PCV	pressure controlled ventilation
P_{dyn}	dynostatic alveolar pressure

PEEP	positive end expiratory pressure
P_{exp}	expiratory pressure
P_{insp}	inspiratory pressure
PSVC	Pressure Regulated Volume Control ventilation
RDS	respiratory distress syndrome
Rfin	resistance at final part of tidal volume middle
Rini	resistance at initial part of tidal volume middle
RM	recruitment manoeuvre
Rmid	resistance at middle part of tidal volume middle
RQ	respiratory quotient
SD	standard deviation
SF_6	sulfur hexafluoride
SLRM	slow, low-pressure recruitment manoeuvre
t_{apne}	apnoea time
TV_{AE}	expiratory alveolar tidal volume
TV_{AI}	inspiratory alveolar tidal volume
V	volume
$\dot{V}$	flow
$\dot{V}A_E$	expiratory alveolar minute ventilation
$\dot{V}A_I$	inspiratory alveolar minute ventilation
$\dot{V}CO_2$	carbon dioxide production
VCO_{2apnea}	amount of CO_2 which was excreted into the alveoli during apnea
VCO_{2pre}	volume of CO_2 in the FRC before the apnea
VCV	volume controlled ventilation
V_D	physiological deadspace,
VDC	volume-dependent compliance
VDR	volume dependent resistance
$\dot{V}_E$	expiratory minute ventilation
V_{exp}	expiratory volume
$\dot{V}_I$	inspiratory minute ventilation
V_{insp}	inspiratory volume
VILI	ventilator induced lung injury
ViCM	vital capacity recruitment manoeuvre
VN_2	volumes of nitrogen
VO_2	volume of O_2
$\dot{V}O_2$	oxygen consumption
$\dot{V}CO_2$	carbon dioxide production
VO_{2apnea}	amount of O_2 taken up from the alveoli during apnea
VO_{2pre}	volume of O_2 in the FRC before the apnea
V_TCO_2	breath-by-breath CO_2 exchange
V_T	tidal volume
V_TO_2	breath-by-breath O_2 exchange
V_TN_2	breath-by-breath N_2 exchange
ZEEP	zero end-expiratory pressure

INTRODUCTION

Acute respiratory failure (ARF) is defined as need for ventilator treatment for more than 24 hours, and is a major reason for admittance to intensive care units for both adults and children. This includes more severe forms of respiratory failure, such as acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), which include criteria concerning increased inhaled oxygen requirement and pulmonary x-ray showing bilateral infiltrates[1].
Mechanical ventilation is lifesaving, but this supportive treatment may also have important side-effects by damaging the lungs and causing ventilator-induced lung injury (VILI). Several mechanisms have been identified as responsible for this, including lung overdistention due to high tidal volume, also known as volutrauma[2], and/or high airway pressures, known as barotrauma[3,4], as well as repeated opening and closure of small airways and alveoli during each breathing cycle, known as atelectrauma[5]. Mechanical lung damage can also lead to local and systemic release of cytokines which contribute to multi-organ failure, and this in the lung has been called biotrauma[6,7].

Mechanical ventilation in adult ARF/ALI and ARDS

It has been shown that if tidal volume is limited to 6 ml/kg ideal body weight and plateau airway pressure is kept below 30 cm H_2O, this may limit or reduce the possible injury associated with mechanical ventilation in patients with ALI and ARDS[8]. Limiting tidal volume and plateau pressure is also a part of the so called ”lung protective strategy”[9], in which global stress and strain on the lungs should be limited[10]. As part of this ”lung protective strategy”, positive end expiratory pressure (PEEP) is adjusted to avoid repeated tidal alveolar collapse and reopening during each breath which could lead to atelecttrauma. Although it has been shown that tidal volume restriction and limitation of airway pressure is beneficial, the optimal level of PEEP has not yet been clearly demonstrated[11-13].

Mechanical ventilation in children and infants with acute respiratory failure

Common reasons for respiratory compromise in infants are meconium aspiration syndrome, group B streptococcal (GBS) pneumonia, congenital diaphragmatic hernia and respiratory distress syndrome (RDS). Lung injury in the neonate develops rapidly and may be manifest already in the delivery room, where the newborn baby may require immediate ventilation. This can occur, in the most urgent phase, with relatively large tidal volumes, high oxygen concentrations, and without positive end-expiratory pressure. Still, modern and optimal newborn resuscitation includes room air ventilation initially and if possible application of PEEP.

Respiratory distress syndrome, RDS, is the most common reason for neonates to need ventilatory support, and they are particularly susceptible to ventilator-associated lung injury due to their very soft, compliant chest cage. Some of these neonatal patients who have RDS and require mechanical ventilation may eventually develop chronic lung disease, including bronchopulmonary dysplasia (BPD). The pathophysiology of RDS include progressive loss of lung volume, intrapulmonary shunt, surfactant dysfunction and alveolar instability[14]. In these patients, a lung protective strategy is extremely important, but also difficult to implement. Surfactant dysfunction makes alveolar units more prone to collapse, leading to repetitive closing and reopening of atelectatic lung during breathing. This atelecttrauma, (alveolar stress) together with high tidal volumes and high airway pressure, may injure the lungs. Recruitment manoeuvres and maintaining lung volume with PEEP can reduce VILI as well as reduce the need for high inhaled oxygen concentrations, which may be toxic especially in small children. In the small child with ventilatory support, there is a high risk of volutrauma, or strain and overstretching to the lung. Infants have compliant chest walls and typically greater distension of the lung, compared to adults, at a given airway pressure, and this adds to the high risk of ventilator-induced overdistension of the lung in small children. The recommended tidal volume to use in order to avoid lung injury, according to the "baby, baby lung concept"[14] in the neonate with RDS is still not generally agreed upon, although a tidal volume of about 6 mL/kg has been recommended. This may not be optimally protective, however, since in theory, if only 1/3 of the lung is available for ventilation, a tidal volume of 6 mL/kg would lead to a lung stretch equivalent of 18 mL/kg in the ventilated part of the lung.

Stress and strain

Gattinoni and coworkers[10,15] proposed that lung stress and strain are the primary determinants of ventilator induced lung injury during mechanical ventilation. These terms are borrowed from bioengineering. Stress is defined as the internal distribution of the counterforce, per unit of area that balances and reacts to an external load. Strain is defined as the deformation of structures, that is, the change in size or shape in relation to the initial status. The clinical equivalent of lung stress for a tidal breath has been suggested to be the transpulmonary pressure (airway pressure minus pleural pressure), while the clinical equivalent of strain is the ratio of tidal volume change and the functional residual capacity (FRC)[10].
The studies emphasises the importance to be able to measure functional residual capacity and end-expiratory lung volume in mechanically ventilated patients.

Functional residual capacity (FRC) and end expiratory lung volume (EELV)

The importance of measuring FRC in patients with acute respiratory failure has been pointed out by several authors including Hedenstierna[16], who in 1993 wrote the following: "relatively few studies have been devoted to develop and refine techniques for bedside lung volume measurements in the mechanically ventilated patient, and to use the lung volume as a guide in treatment of the patient and setting the ventilator".
Functional residual capacity (FRC) is generally recognised as the lung volume at the end of a normal expiration during tidal breathing when there is no application of positive end-expiratory pressure (PEEP). It has been defined as the relaxed volume of the lungs at equilibrium (resting, no breathing activity or airflow) when there is no respiratory muscle activity and no pressure difference between alveoli and atmosphere[17]. Reference values for FRC have been for the most part obtained from spontaneously breathing patients in the standing or sitting position[18,19]. However, FRC measurements can be performed during non-resting circumstances, including increased end-expiratory pressure.
The term end-expiratory lung volume (EELV)[20-22] can be used to describe the lung volume where PEEP is applied during mechanical ventilation. In this thesis the term FRC is also used, even when PEEP is applied, usually with a notification of the PEEP level used. Today both expressions are used in the literature.

Methods for FRC/EELV measurements

Dilution techniques:

The dilution method for determining lung volumes was first described by Davy 1800[23] and then later further modified[24-27]. This technique is based on the delivery of a known volume of a poorly soluble tracer gas, such as H_2, SF_6, He, N_2, Argon, Xenon-133, or O_2, to a breathing circuit of known volume. After equilibration in the lungs, in the FRC, the concentration of the inhaled inert gas is measured. The FRC is calculated as the volume of delivered inert gas at a known concentration/fraction of inert gas. The dilution will only take place in ventilated lung regions, and "trapped gas" in the lung will not be included when these techniques for FRC measurements are used[28].

Closed-circuit method
Helium dilution

Because of the danger of explosion with hydrogen-oxygen mixtures, Meneely et al.[29] replaced the formerly used hydrogen gas with helium. The technique has been further modified[30] and simplified by Heldt et al.[31] who used a bag-in-box with a valve, making it possible to maintain mechanical ventilation during FRC measurements.
The measurements are started at end-expiration, and mean airway pressure and PEEP are maintained unchanged so that mechanical ventilation can be continued at the same tidal volume and frequency. The helium-containing bag is enclosed in a rigid box. The airway is connected to the bag, and the inspiratory volume of the ventilator is diverted into the plastic box, emptying the helium-containing bag into the patient´s lungs. The pressurized gas in the box is eliminated through the ventilator during the expiratory cycle when the patient exhales into the rebreathing bag. The closed-circuit helium dilution technique has been used in several clinical studies[30-34]. It is a demanding technique which requires considerable operator training, bulky instruments, and precision with O_2 addition and CO_2 removal. These factors make it unsuitable for general clinical practice. This technique requires only slow response gas analyzers since the measurements of gas concentrations are only performed before and after rebreathing. A disadvantage is that free-standing ventilators traditionally are not designed with a rebreathing system, and therefore need substantially modifications for FRC measurements.

Recently, Patroniti et al.[35] evaluated a simplification of the method, which involved clamping a flexible tube during an end-expiratory pause, connecting the patient to a 1.5 L balloon with He gas mixture, and then manually ventilating the patient with the mixture. The concentration of helium in the balloon after the procedure was then measured and FRC calculated. Subsequent studies show that this technique has a good correlation with CT scan for FRC assessment, although there is an underestimation with the helium technique which increases with increasing lung volumes[22]. When the patient is disconnected from the ventilator for this measurement, they are exposed to risk for alveolar derecruitment due to no PEEP during measurement, which also potentially affects observed FRC values.

Open multiple breath procedures

Sulfur hexafluoride (SF_6)

Instead of collecting expired gas in a bag Jonmarker[36], and Larsson[37] arrived at the volume of washed-out tracer gas using measurements of tracer gas concentrations and expired flow. They used a sensitive and rapid response infrared SF_6 analyzer which permits measurement of tracer gas at concentrations below 0.5%. SF_6 wash-in is continued at a constant rate until there is no detectable change in expired SF_6 concentration over a period of 1 min. Mean expired SF_6 concentration is only 0.001%.
East et al.[38] described a method that could be used with any mode of mechanical ventilation as well as with spontaneous breathing without interruption of ventilation. They used a SF_6 delivery system that maintained inspired concentration of SF_6 at a constant 0.5% regardless of inspiratory flow. The SF_6 technique has recently been used in clinical research studies[39-41] though it is not approved for clinical use.

Direct measurements of N_2 washout by N_2 analysis in adults

Durig et al.[42] described the nitrogen dilution technique already in 1903, and a further refinement with the open circuit nitrogen washout method was presented in 1940[43]. During open circuit multiple breath nitrogen washout (MBNW) for measurement of FRC, the inspiratory fraction of oxygen (F_IO_2) was changed from baseline to 1.0 to wash out all nitrogen from the lungs. Thereafter, F_IO_2 is changed back to the baseline value, and N_2 is washed in again. The equipment historically has been bulky and obviously there is a limitation for use in critically ill patients ventilated with already high F_IO_2. To permit a smaller step change in

inspired N_2 fraction without interruption in mechanical ventilation, the use of two synchronized volume ventilators was proposed though only used in laboratory conditions[44].

A nitrogen analyzer and a respiratory flow transducer were integrated into a computerized system used by Ibanez et al.[18,45]. The patient was manually ventilated with air for several breaths by compressing a bag. At the end of expiration there was a switch to the ventilator and 100% oxygen until alveolar concentration of nitrogen was less than 1%. One problem with this technique was that the change in gas viscosity during the washout manoeuvre affects the accuracy of the gas flow measurement by pneumotachography.

Wrigge et al.[46] obtained acceptable accuracy when using a continuous viscosity correction of mass spectrometer delay time relative to gas flow signal. Gas concentrations were measured in a sidestream analyzer, in the attempt to get a more accurate synchronization of gas analysis and flow. To reduce the influence of N_2 washed out from body tissues and of signal noise, the calculation from the measurement was completed at 3% of the baseline F_{N2} and a correction for tissue N_2 was used[47]. The volume of nitrogen that enters the lung during the first breath after the change in F_IO_2 was also corrected for when calculating the total amount of nitrogen washed in or out, a technique also used in later studies[48,49].

Direct N_2 washout measurements of FRC in children and infants

Measurements of FRC by N_2 washout have been frequently used in the paediatric clinical research both in spontaneously and mechanically[50-56] breathing children. Sjöqvist et al.[50] described a method where airflow was measured by volume displacement with a body plethysmograph instead of through the endotracheal tube. This N_2 washout technique circumvented the problem with leakage at the endotracheal tube since this gas has the same concentration of nitrogen as the gas sampled at the Y-shaped connector[56]. But when using two ventilators, the operator needs to switch over from the baseline ventilator to the washout ventilator precisely at end-expiration, that is, when the lung volume and the respiratory cycle are at FRC.

Sivan et al.[51] presented an automated bedside method that assumed that the average gas flow over time remains constant. They measured minute volume of ventilation both during calibration and during the test. Two ventilators were needed, with a three-way valve, to be able to direct only the gas exhaled from the patient, without the baseline flow in the system, in order to reduce the amount of N_2 free gas in which lung gas is diluted in small ventilated children who have only a small amount of N_2 in the lungs. The technique cannot be used in patients with

high oxygen concentrations, and the technique has later been shown to have problems with unstable values over time which require correction[57].
The need to increase oxygen concentration to 100%, when using these methods, leads to potential risk of clinical oxygen toxicity and atelectasis formation. In addition, these techniques are not practically possible to use in children who are already on high inspired oxygen concentrations.

Indirect measurements of N_2 washout by O_2 and CO_2 analysis

To overcome problems of measuring N_2 directly, Mitchell et al.[58] described a technique to measure FRC by using the open-circuit N_2 washout principle with oxygen as the indicator gas, as well as calculating N_2 concentration indirectly as the residual of O_2 and CO_2 measurements using online O_2 and CO_2 analyzers. Fretschner et al.[59] used "rapid" mainstream CO_2 analyser, a "slow side-stream" O_2-analyzer, and a pneumotachograph. They changed F_IO_2 from 70 to 100% and from 100 to 70%, and performed breath-by-breath calculation of nitrogen concentration which then was synchronized with flow from a pneumotachograph. Total inspired and expired volumes of nitrogen (VN_2) were derived from measurements of total inspired and expired CO_2 volume (VCO_2), and O_2 volume (VO_2) only. A fast mainstream CO_2 analyzer was needed since this is the basis for the transformation of the O_2 signal, which is computed from the measured inspired and expiratory O_2-maximum/-minimum values and the fast CO_2-curve. The net transfer of nitrogen per breath can then be summed over the washout/wash-in procedure, and FRC calculated. The method is sensitive to baseline drift concerning flows, which needs to be assessed and corrected. The accuracy of the method is limited by the rise time of the oxygen sensor, and synchronization is very sensitive. Small errors may lead to large miscalculations of N_2. The method is simpler to perform, but less precise than the previously used N_2 washout techniques, and has an error of 20%, which is more than earlier methods.
Eichler et al.[60] simplified the method further and used the flow probe of the ventilator instead of an external pneumotachograph. The ventilator was equipped with mainstream analyzers for CO_2 and O_2, to circumvent the problem with slow O_2 sensors. They used a step change of F_IO_2 from 0.3 to 1.0, though this makes the method impossible to use in critically ill patients with high inspired oxygen levels. Recently, Weismann et al.[61] further simplified the technique by using a model that calculates the flow-dependent delay time of the side-stream O_2 analyzer, to facilitate synchronization of the oxygen concentration and gas flow signal. Therefore, a mainstream CO_2 analyzer is no longer required to separate inspiration and expiration. The technique (LUFU) uses software installed on a personal computer which is connected to the commercial ventilator, (Evita 4,

Draeger), from which it continuously acquires airflow, volume, and airway pressure. This method has been tested during spontaneous breathing[62,63] and during controlled and assisted mechanical ventilation[64,65]. This method is not yet available for routine clinical use.

Computed Tomography Scan, CT scan

CT scanning has previously been considered to be the reference technique for FRC measurements. The CT method measures the volume of the whole "anatomical lung" and not necessarily the volume of the "functional lung" which takes part in the gas exchange. When there are lung regions with non-ventilated or trapped gas, the volume of the anatomical lung will be different from the functional lung. The technique has been used in several clinical studies[35,41,66]. Rylander et al.[41] found a 34% lower functional lung volume measured by rebreathing of SF_6 compared to CT anatomic estimation,while Patroniti et al.[35] found acceptable bias and limits of agreement between CT and He dilution techniques in mechanically ventilated patients.
The CT is not practical for frequent bedside measurements since it requires transportation away from the intensive care unit in most hospitals. Because of radiation dose with each CT examination, frequent FRC measurements are not advisable.

Body plethysmography

The body plethysmographic method for FRC measurements (FRC_{pleth}) was described first in 1956[67]. FRC_{pleth} refers to the intrathoracic gas volume measured when airflow occlusion occurs at FRC. The method is based on Boyle´s law which states that the volume of gas varies in inverse proportion to the pressure applied (under constant temperature). In other words, the product of volume and pressure at any given moment is constant[68]. The patient sits in an airtight body box, and measurements are taken at end-expiration (or end-inspiration). When there is no air flow, the alveolar gas is known to be at ambient barometric pressure. When breathing is stable and the end-expiration near FRC, a shutter is closed for 2-3 seconds and the patient performs gentle sighs at a frequency of 1-2 per second. A smaller box interior provides a better signal, and the measurements cannot begin until interior of the box warms to approximately body temperature. This technique is not practical for use in mechanically ventilated patients.

Assessment of lung recruitment in acute lung injury

Alveolar recruitment is an important part of the respiratory management in patients with acute lung injury (ALI) and Acute Respiratory Distress Syndrome (ARDS), and is used to improve gas exchange as well as to protect the lungs from ventilator-induced lung injury. Successful recruitment of lung areas to participate in ventilation and gas exchange where they were previously not participating typically leads to improved oxygenation, increase in lung compliance, increase of end expiratory lung volume (EELV), and a decrease in end-tidal carbon dioxide tension. It should be noted that an increased EELV per se is not necessary a result of lung recruitment but can also occur due to over-inflation of already inflated alveoli. Compliance measurements may help to determine if an increase in EELV is due to recruitment or over-inflation, since an increase in compliance following a recruitment manoeuvre can almost only be a result of alveolar recruitment. Compliance measurements normally require an end-inspiratory 'hold' or pause to achieve static or quasi-static conditions, depending on the duration of the 'hold'. This makes these compliance measurements unsuitable to use during ongoing ventilation in patients[69]. Experimental and clinical studies have shown that classical two point compliance measured during ongoing ventilation in volume control mode with a short end-inspiratory pause maybe used to define optimal PEEP after a recruitment manoeuvre[70,71]. Two point compliance is the average compliance of a breath. If one uses techniques to obtain alveolar pressure-volume curves during ongoing ventilation, such as the SLICE-method[72] or the Dynostatic algorithm[73], it has been shown that alveolar compliance is not constant over the whole breath[74-76]. Indeed, using these alveolar pressure-volume curves, changes in compliance within each breath could be calculated[74,75], for the initial (Cini) middle (Cmid) and final parts of the breath (Cfin), instead of calculating just an average value[71]. In a study in isolated rabbit lungs, it was proposed to use volume-dependent compliance (VDC) as a basis to adjust positive end-expiratory pressure (PEEP)[77]. Similarly, airway resistance can be calculated during a single breath, and previous studies indicate that resistance may vary considerably, not only for the large volume ranges but also within the breath[78].

The clinical problem

Knowledge of FRC/EELV at the bedside would be an important tool, together with gas exchange and lung mechanic parameters such as respiratory compliance and resistance, for early quantification and limitation of unnecessary "lung strain" leading to ventilator induced lung injury (VILI)[10]. Lung volume measurements would also be valuable to monitor the effects of therapeutic interventions such as lung recruitment manoeuvres, PEEP titration, and in newborns surfactant instillation. Earlier methods for lung volume measurements are difficult to apply at the bedside[60,79]. They require bulky measurement equipment and/or advanced techniques for gas analysis. Special tracer gases such as SF_6 may be needed, which are not available for general clinical use. Some research groups suggests that CT scanning should be considered as a "gold standard" although CT allows measurement only of the whole anatomical lung and not the functional lung volume[22]. Furthermore, this technique can only be very occasionally used in ICU patients since they need to be transported and because the relatively large radiation exposure would not allow serial measurements. A clinically useful method for monitoring FRC/EELV at the bedside, combined with non-invasive techniques such as volume-dependent compliance, would provide the clinician with more comprehensive information concerning lung function at the bedside to guide ventilatory management in intensive care patients.

AIM OF THIS THESIS

- To develop and evaluate clinically useful bedside methods to measure functional residual capacity (FRC) and end expiratory lung volume (EELV) in mechanically ventilated adults and small children (Paper I, II, III).

- To evaluate the combined use of FRC/EELV measurements and volume-dependent compliance to assess the effects of lung recruitment manoeuvres in an experimental lung lavage animal model (Paper IV).

METHODS

ETHICAL ISSUES

The studies were approved by The Regional Ethical Review Board of Gothenburg, and signed consent obtained from the patients or next of kin. The animal study in paper IV was approved by the Committee for Ethical Review of Animal Experiments at Gothenburg University.

PATIENTS AND ANIMALS

PATIENTS (I, II, III):

Paper I:

Six patients with acute respiratory failure were studied, and these were ventilated with a Servo 900C ventilator in volume control mode.

Paper II:

Twenty-eight patients were studied, and these were endotracheally intubated and mechanically ventilated at the Intensive Care Department, either postoperatively or due to respiratory insufficiency. A Servo 900C or 300 ventilator (Siemens/Maquet, Solna, Sweden) was used.

Paper III:

Ten children without cardiopulmonary disease undergoing non-thoracic surgery were studied peri-operatively during inhalational (without nitrous oxide) or total

intravenous anaesthesia (Table 1). Cuffed endotracheal tubes were used. The children were treated with muscle relaxants and ventilated according to departmental routines as part of their peri-operative care. The Datex-GE Anaesthesia Delivery Unit (ADU) was equipped with a breathing circuit, type Mapleson D. In the intensive care unit, six children were ventilated for postoperative respiratory insufficiency. They were sedated without muscle relaxants or cuffed endotracheal tubes.

Table 1. Patient Characteristics:

ID	Age, months (m), days (d)	Diagnosis	Operation	Weight, kg
1	1 m	Hydronephrosis	Pyeloplastic	4.9
2	6 m	Cystic kidney	Circumcision	7.6
3	12 m	Index duplex	Extirpation	8.6
4	7 m	Fibular anomaly	Osteotomy	8.7
5	16 m	Apert's Syndrome	Syndactyli separation	11.6
6	11d	Mb Hirshsprung	Bowel resection	4.4
7	20 m	Hypoplastic kidney	Nephrectomy	12.5
8	37 m	Shoulder anomaly	Subscapular tendon elongation	14.2
9	22 m	Hypospadia	Correction	14.7
10	62 m	Mb Perthes	Femoral osteotomy	20
11	2 m	Atrioventricular Septum Defect	ICU	3.6
12	56 m	Duodenal Hemorrhage	ICU	18
13	7 m	Ventricular Septum Defect	ICU	6.1
14	10 d	Transposition of Great Arteries	ICU	3.5
15	11 d	Ligation of Ductus Arteriosus. Persistens	ICU	1.9
16	6 m	Atrioventricular Septum Defect	ICU	4.1

ANIMALS (IV):

Fourteen Swedish landrace pigs of either gender (25-30 kg) were used and care for in accordance with the NIH guidelines for the care and use of laboratory animals[80]. The pigs were anesthetised, placed in supine position, tracheotomised, and mechanically ventilated.

EXPERIMENTAL MODELS

MECHANICAL LUNG MODELS (I, II, III):

Paper I-II:

The 'metabolically active' lung model used in our study[81,82] has gases with the same humidity and temperature as airway gases of the patients. The lung model consisted of a single "alveolus" with the possibility for combustion of hydrogen (Fig 1).

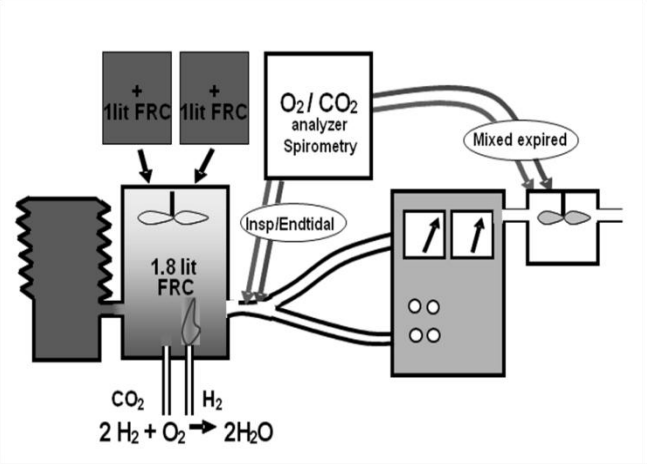

Figure 1: In Paper I-II, functional residual capacity (FRC) measurements were validated in an oxygen (O_2) consuming / carbon dioxide (CO_2) producing lung model by combustion of hydrogen and adding CO_2. Respiratory quotient (RQ), lung model volume, breathing frequency and minute volume could be varied. Gas analysis and ventilation volumes were analyzed with a standard side stream monitor.

Carbon dioxide (CO_2) output was achieved by delivery of CO_2 into the "alveolus" using a precision electronic flow controller. Oxygen (O_2) consumption was achieved by combustion of hydrogen in a mini-Bunsen burner where $2H_2 + O_2 = 2H_2O$, that is, the O_2 consumption equals half of the delivered volume of hydrogen. The hydrogen flow was controlled by an electronic flow regulator.
The respiratory quotient (RQ), which is the ratio $\dot{V}CO_2 / \dot{V}O_2$, was managed by adjusting the settings of $\dot{V}CO_2$ and $\dot{V}O_2$ of the lung model **(I-II)**. The basal FRC of the lung model was 1.6 L **(I)** or 1.8 L **(II),** and was increased stepwise by adding volume to the single alveolus.

Paper III:

The paediatric lung model consisted of a container where the volume was managed by adding water. Carbon dioxide was delivered to the container with a constant flow. A miniature fan was used for mixing of gas. The CO_2 flow was verified with an Alltech flowmeter with a precision of ± 2%. Two respiratory circuits were tested in the model. In the anaesthesia setup, a Mapleson D breathing system was connected to the anaesthetic machine. In the ICU setup, a Servo 300 ventilator was used, with a small calibre, low compliance tubing. The congruence of the $\dot{V}CO_2$, calculated by the monitor and the CO_2 flow to the lung model, was aligned by introducing different sizes of spacers between gas-sampling and the y-piece.

LUNG INJURY MODELS (IV):

An experimental model of acute lung injury (ALI) was established in the pig by repeated broncho-alveolar lavage (BAL) with body warm saline, 30 ml/kg in each wash, resulting in surfactant depletion, atelectasis, and impaired gas exchange[83]. The total amount of saline used for this ranged from 9-15 litres. During the procedure the animals were ventilated in volume-controlled mode with PEEP 10 cmH_20 and F_IO_2 1.0. BAL was continued until there were no visual signs of surfactant in the fluid exchange and PaO_2 was less than 10 kPa or oxygen saturation was below 90% at F_IO_2 1.0. The animals were allowed to stabilise for one hour, and if oxygenation improved, additional lavage was performed.

MEASUREMENTS AND CALCULATIONS:

Paper I:

Current methods for determination of FRC are based on wash-in/wash-out of low soluble gases. We chose to use the physiological wash-in/wash-out of metabolic gases carbon dioxide (CO_2) and oxygen (O_2) during a short apnoea.
The methodological setup for measuring FRC by quantifying O_2 and CO_2 fluxes during an apnoeic period is shown in Fig 2.

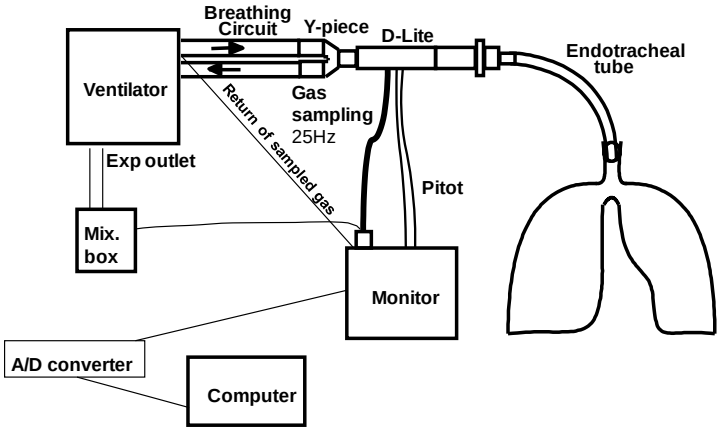

Figure 2: Ordinary clinical monitoring equipment with fast side stream O_2 and CO_2 analyzers. Inspiratory and end-tidal gas concentrations and flow volumes were collected breath-by-breath through a side stream spirometer, D-light. Mixed expiratory O_2 and CO_2 concentrations were registered in steady state from a 5 L mixing box. Collected gases were rebreathed to the circuit. The gas concentrations and flow volumes were sampled at a frequency of 25 Hz and digitalized via an A/D converter and calculations were performed manually in a personal computer with a customized soft ware program (Testpoint).

During a short apnoea, gases are exchanged continuously between alveoli and lung capillaries, which leads to wash-in of CO_2 from the blood to the alveoli and wash-out of oxygen from the alveoli to the blood (Fig 3). During an apnoeic interval, the O_2 tension falls approximately 1-2 kPa. But, as seen on the O_2 dissociation curve, the lung capillary oxygen content is basically unchanged because the haemoglobin is equally saturated at these levels. This leads to an almost unchanged O_2 wash-out to the blood. In contrast, the CO_2 solubility and content in the blood increases with the CO_2 tension during the apnoea. This leads to a decrease of wash-in of CO_2 to the alveoli during the apnoea. This is corrected for in the formula for calculation of FRC.
The principle for the measurements is shown in Fig 4.

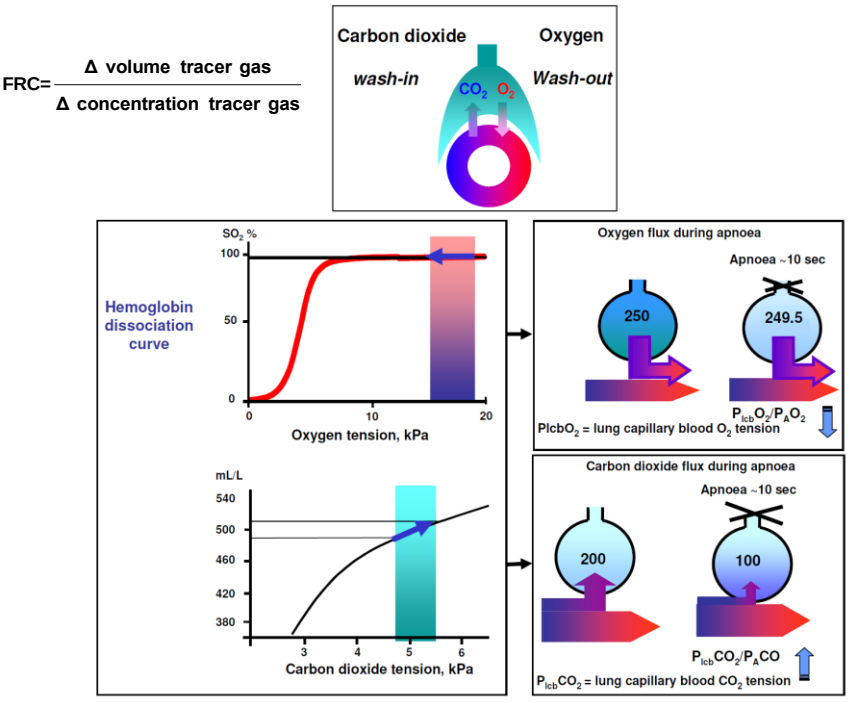

Figure 3: During a short apnoea, gas exchange continues, resulting in wash-in of CO_2 from blood to the alveoli and wash-out of oxygen. By monitoring changes in end-tidal CO_2 and O_2 after apnoea, FRC can be calculated (see fig 5). During apnoea, lung capillary oxygen content is unchanged, while carbon dioxide content increases. FRC can be calculated from changes in O_2 and CO_2 during a short apnoea after correction for changes in CO_2 solubility in blood.

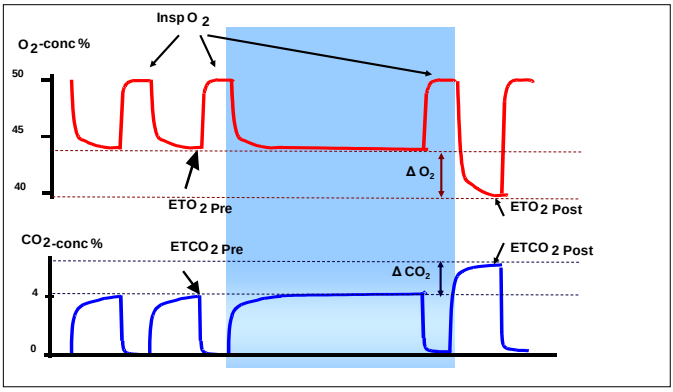

Figure 4: O_2/CO_2 flux FRC (FRC_{flux}) measurements were obtained by analysis of changes in oxygen (ΔO_2) and carbon dioxide concentrations (ΔCO_2) before and after an 8-15 second apnoea. Larger change in gas concentrations corresponds to lower FRC_{flux}. Base-line oxygen uptake and carbon dioxide output were measured by indirect calorimetry. End tidal oxygen concentration before apnoea (ETO_{2Pre}), and after apnoea (ETO_{2Post}). End tidal carbon dioxide concentration before apnoea ($ETCO_{2Pre}$), and after apnoea ($ETCO_{2Post}$). Inspiratory oxygen (Insp O_2).

Breath-by-breath analysis of inspiratory and end-tidal (alveolar) concentrations of O_2 and CO_2 were used both before and after an 8-15 second apnoea. FRC was then calculated from the change in O_2 and CO_2 during the apnoea, and larger change in the concentrations of these gases meant smaller FRC. The end-tidal values of O_2 and CO_2 before (pre) and after (post) the apnoea gives the four formulas which are the basis for the flux method for FRC measurements (Fig 5).

FRC_{flux} algorithm with correction for CO_2 solubility in blood

1. $$FETO_{2pre} = \frac{VO_{2pre}}{FRC}$$

2. $$FETCO_{2pre} = \frac{VCO_{2pre}}{FRC}$$

3. $$FETO_{2post} = \frac{VO_{2pre} + TV_{AI} \times FIO_2 - VO_{2apnoea}}{FRC + TV_{AE} - LCBCO_2}$$

4. $$FETCO_{2post} = \frac{VCO_{2pre} + VCO_{2apnoea} - LCBCO_2}{FRC + TV_{AE} - LCBCO_2}$$

Functional Residual Capacity, FRCflux

$$\frac{(FETCO_{2post}-1)(TV_{AI} \times FIO_2 - VO_{2apnoea}) + FETO_{2post}(TV_{AE} - VCO_{2apnoea})}{FETO_{2post}(FETCO_{2pre}-1) + FETO_{2pre}(1-FETCO_{2post})}$$

$LCBCO_2$ = lung capillary blood carbon dioxide

Figure 5: The O_2/CO_2 flux FRC (FRC_{flux}) algorithm is based on four equations. 1: Alveolar O_2 concentration before the apnoea ($FETO_{2pre}$) = O_2 amount in alveoli before apnoea (VO_{2pre})/volume of alveoli (FRC). 2: The alveolar CO_2 concentration before the apnoea ($FETCO_{2pre}$) = CO_2 amount in alveoli (VCO_{2pre})/ volume of alveoli (FRC). 3: Alveolar O_2 concentration after apnoea ($FETO_{2\ post}$) = [VO_{2pre} + volume of O_2 in the first inhalation (inspiratory alveolar tidal volume (TV_{AI})*FIO_2) – O_2 uptake in blood ($VO_{2apnoea}$)] / Total lung volume before expiration [FRC + expiratory alveolar tidal volume (TV_{AE}) + CO_2 volume dissolved in blood ($LCBCO_2$)]. 4: Alveolar CO_2 concentration after apnoea ($FETCO_{2post}$) = (CO_2 amount in alveoli before apnoea + volume of CO_2 in to alveoli during apnoea – CO_2 volume dissolved in blood) / Total lung volume before expiration (FRC + TV_{AE} + CO_2) volume dissolved in blood). The four equations lead to the final calculations of FRC_{flux}.

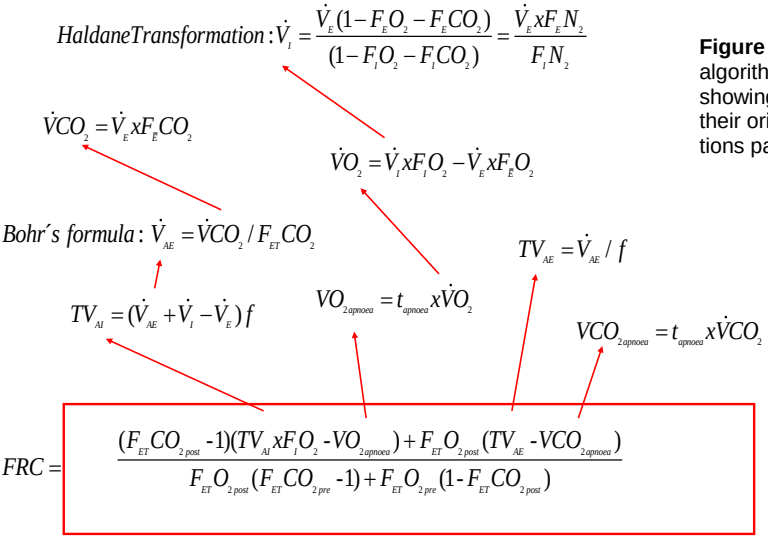

Figure 6: The FRC flux algorithm with arrows showing the analysis and their origin. See abbreviations page *ix*.

The measurements start at steady state and via a mixing box, with determination of oxygen consumption and carbon dioxide production by indirect calorimetry[82,84]. Inspiratory alveolar tidal volumes (TV_{AI}), expiratory alveolar tidal volumes (TV_{AE}), and respiratory rate (f) are then measured.
Oxygen consumption, $\dot{V}O_2 = \dot{V}_I \times F_IO_2 - \dot{V}_E \times F_{\bar{E}}O_2$, and carbon dioxide production, $\dot{V}CO_2 = \dot{V}_E \times F_{\bar{E}}CO_2 - \dot{V}_I \times F_ICO_2$, are calculated, where $F_{\bar{E}}O_2$ and $F_{\bar{E}}CO_2$ are the mixed expiratory concentrations of O_2 and CO_2 respectively and the F_ICO_2 was assumed to be zero.

The inspiratory minute volume ($\dot{V}_I$) was calculated by Haldane transformation with the assumption that there was no net exchange of nitrogen.

Expiratory alveolar minute ventilation ($\dot{V}A_E$) was calculated by Bohr´s formula, where $F_{ET}CO_2$ was the alveolar/end-tidal concentration of carbon dioxide.
The inspiratory oxygen concentration, F_IO_2, and end-tidal oxygen and carbon dioxide concentrations were measured during the last tidal breath before apnoea ($F_{ET}O_2$pre and $F_{ET}CO_2$pre). Apnoea was instigated by an 8-15 seconds (t_{apnoea}) end-expiratory paus.
End-tidal oxygen and carbon dioxide fractions ($F_{ET}O_2$post and $F_{ET}CO_2$post) of the exhalation from the first breath after cessation of the expiratory hold were measured. This breath was of the same volume as the last breath before the apnoea. The amount of O_2 taken up from the alveoli during the apnoea (VO_2 apnoea) was calculated as the product of the apnoea time, t_{apnoea} and the $\dot{V}O_2$. The amount of CO_2 which was excreted into the alveoli during the apnoea ($VCO_{2apnoea}$) was calculated. The true wash-in of CO_2 to the alveoli during the apnoea ($VCO_{2apnoea}$) was however lower; this as a result of the increased amount being dissolved in lung capillary blood (LCB) due to increased partial pressure of CO_2 in lung capillaries caused by the apnoea. The $LCBCO_2$ is the part of the VCO_2 apnoea that will remain in the pulmonary capillary blood during the apnoea. This is a result of the increase in alveolar/pulmonary capillary CO_2-tension, where the VO_{2pre} and VCO_{2pre} are the volumes of O_2 and CO_2 in the FRC before the apnoea[17] (Fig 5). In the final FRC formula, the $LCBCO_2$ disappears in the equation. The original calculations in the formula are shown in Fig6.

Paper II, III:

We have developed a new algorithm for nitrogen (N_2) multiple breath washout (NMBW) using standard clinical O_2 and CO_2 sensors and flow meters to minimize the step change in O_2. The setup for measuring FRC by N_2 wash-out/wash-in technique is shown in Fig 7.

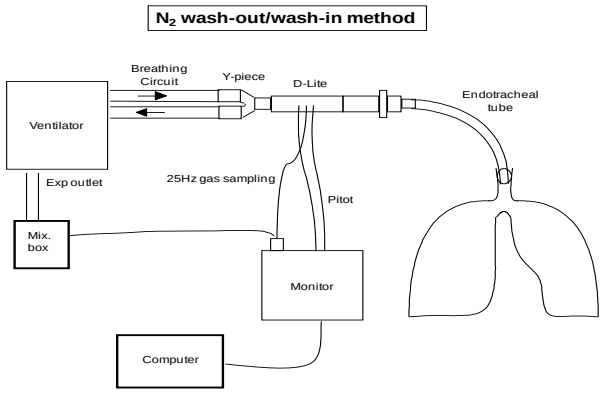

Figure 7: The N_2 wash-out/wash-in method for FRC measurements (FRC_{N2}) used similar equipment as the FRC_{flux} method, except that there was no need to return collected gases to the circuit and no need for an A/D converter.

In the same way as other gas dilution methods, the NMBW method is based on wash-in/wash-out of a known amount of gas with a known concentration, which is diluted in the lung. The resulting expired gas concentration can be measured after a new steady state is reached, which allows calculation of FRC (Fig 8). The oxygen consumption, $\dot{V}O_2$, and carbon dioxide production, $\dot{V}CO_2$, were calculated via a mixing box as in Paper I. In Paper III, the carbon dioxide production ($\dot{V}CO_2$) was obtained from the gas analyzer of the monitor (COMVX, S/5, GE Health Care, Helsinki, Finland) (Paper III). The indirect calorimetric measurements of $\dot{V}CO_2$ for the modified method are replaced by a default value for $\dot{V}CO_2$ based on body weight and the Brody formula for oxygen consumption[85], with $\dot{V}O_2 = 10 \times kg^{3/4}$ in combination with a default value for the respiratory quotient of 0.85: Default $\dot{V}CO_2 = 0.85 \times 10 \times kg^{3/4}$ (Paper III).

Expiratory alveolar minute ventilation ($\dot{V}A_E$) was calculated according to Bohr's formula: $\dot{V}A_E = \dot{V}CO_2 / F_{ET}CO_2$, assuming equality of end-tidal carbon dioxide fraction ($F_{ET}CO_2$) and alveolar CO_2 (Papers II, III).

The inspiratory alveolar minute ventilation ($\dot{V}A_I$) was calculated as the difference between inspiratory minute ventilation ($\dot{V}_I$) and expiratory minute ventilation ($\dot{V}_E$) plus the expiratory alveolar minute ventilation:

$\dot{V}A_I = \dot{V}A_E + \left(\frac{V_TCO_2}{RQ} - V_TCO_2 \right)$. The respiratory quotient (RQ) is defined as $RQ = \frac{V_TCO_2}{V_TO_2}$ (Papers II, III).

The inspiratory and expiratory alveolar tidal volumes (TV_{AI} and TV_{AE}) were calculated from the alveolar minute ventilation and the respiratory rate.
Breath-by-breath N_2 exchange (V_TN_2) was calculated as the difference between inspired and expired N_2 volume after a fractional step change in F_IO_2:

$$V_TN_2 = (F_IN_2 \times TV_{AI}) - (F_{ET}N_2 \times TV_{AE})$$

where F_IN_2 = 1 - F_IO_2, and $F_{ET}N_2$ = 1 - $F_{ET}O_2$ - $F_{ET}CO_2$. F_IN_2 is the inspiratory N_2 fraction, $F_{ET}N_2$ is the end-tidal N_2 fraction, and $F_{ET}O_2$ is the end-tidal O_2 fraction. The inspiratory and end-tidal O_2 and CO_2 concentrations were acquired breath-by-breath from the monitor output (Papers II, III).
The alveolar FRC (FRC_{alv}) was calculated according to the following:

$$FRC_{alv} = \frac{\sum V_TN_2}{F_IN_{2ini} - F_IN_{2end}}$$

where (F_IN_{2ini} - F_IN_{2end}) is the difference in inspiratory N_2 concentration between start and end of washout (Papers II, III). Summary of FRC calculations of N_2 wash-out/wash-in is shown in Fig 9.

$$FRC = \frac{\Delta \text{ volume tracer gas}}{\Delta \text{ concentration tracer gas}}$$

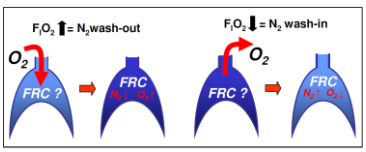

Figure 8: N_2 wash-out and wash-in for FRC measurements by only using a step change of inspiratory oxygen fraction (F_IO_2) of 0.1.

1. Oxygen consumption	$\dot{V}O_2 = F_IO_2 \times \dot{V}_I - F_EO_2 \times \dot{V}_E$	
2. Inspiratory minute ventilation	$\dot{V}_I = \dot{V}_E(1 - F_EO_2 - F_ECO_2)/(1 - F_IO_2 - F_ICO_2)$	
3. Carbon dioxide production	$\dot{V}CO_2 = \dot{V}_E \times F_ECO_2$	
4. Alveolar minute ventilation	$\dot{V}_{AE} = \dot{V}CO_2 / F_{ET}CO_2$	$\dot{V}_{AI} = (\dot{V}_I - \dot{V}_E) + \dot{V}_{AE}$
5. Tidal alveolar ventilation	$TV_{AE} = \dot{V}_{AE}/f$	$TV_{AI} = \dot{V}_{AI}/f$
6. Inspiratory nitrogen fraction	$F_IN_2 = 1 - F_IO_2$	
7. End-tidal nitrogen fraction	$F_{ET}N_2 = 1 - F_{ET}O_2 - F_{ET}CO_2$	
8. Volume nitrogen washed in	$V_{N_{2in}} = \sum_{0\text{-}3tc} TV_{AI}(F_IN_2 - F_{ET}N_2)$	
9. Volume nitrogen washed out	$V_{N_{2out}} = \sum_{0\text{-}3tc} TV_{AE}(F_{ET}N_2 - F_IN_2)$	
10. Change in nitrogen fraction during washout/washin	$\Delta F_{N_2} = F_IN_{2initial} - F_IN_{23tc}$	
11. Functional Residual Capacity (*tc = time constant*)	$FRC = \Delta V_{N_2} / \Delta F_{N_2}$	

Figure 9: Summary of calculations leading to FRC by N_2 wash-out/ wash-in technique.
Values obtained from monitors gas sampling in red, from ventilator spirometry in green, and from mixing box in blue. (See abbreviations page *ix*).

The principle for measurement procedure is shown in Fig 10.

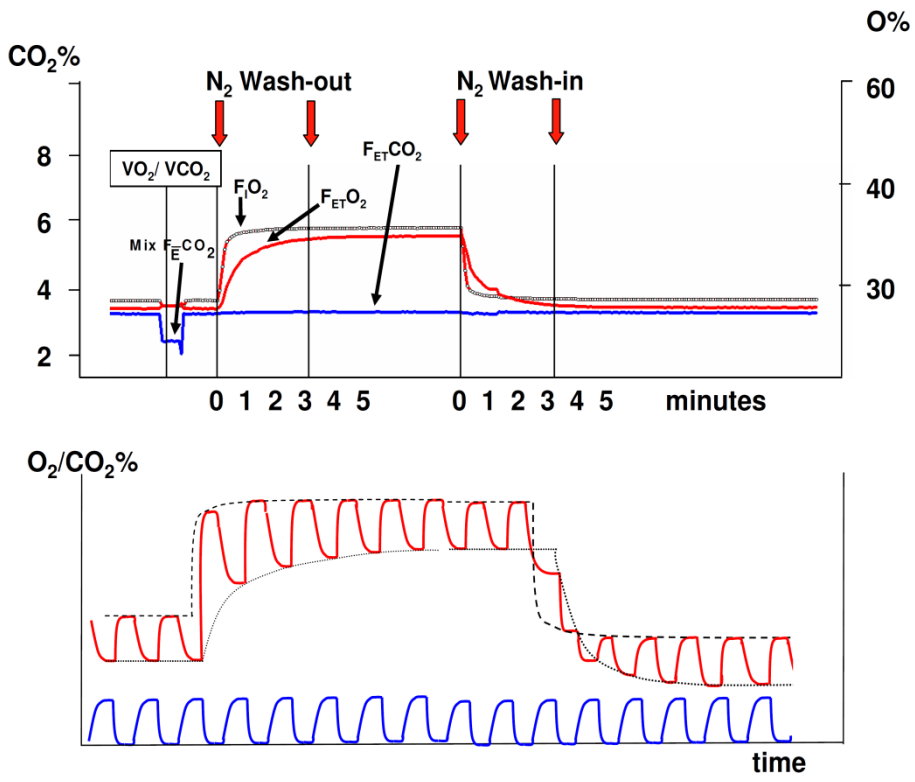

Figure 10: Analysis of one wash-out/wash-in FRC measurement is started by measuring O_2 consumption ($\dot{V}O_2$) and CO_2 production ($\dot{V}CO_2$) by indirect calorimetry and sampling of mixed expiratory fraction of carbon dioxide (Mix F_ECO_2) from a mixing chamber (see fig.2).
Wash-out of N_2 is achieved by raising inspiratory fraction of oxygen (F_IO_2), and wash-in of nitrogen (N_2) is achieved by decreasing F_IO_2. The red line shows the F_IO_2 and end tidal O_2 ($F_{ET}O_2$) and the blue line shows the end tidal CO_2 ($F_{ET}CO_2$). We avoided the problem of synchronization of flow and gas analysis by measuring end-tidal data from O_2, CO_2 concentrations breath by breath.

The classical definition of FRC, which includes the airways from alveoli to mouth, is calculated as: $FRC = FRC_{alv} + V_D/RR$, where the physiological dead-space, $V_D = \dot{V}_E - \dot{V}A_E$

Both in the lung model and in patients, each wash-out or wash-in procedure was analyzed during 3 time constants, which is equivalent to 95% of a complete wash-in or wash-out effect. This corresponded to a duration of about 80-120 s (Paper II).

Paper IV:

Tracheal pressure was measured with a fluid filled pressure line inserted into the tracheal tube and positioned two cm below the tip of the endotracheal tube[73,74]. The pressure sensor was placed so that the tracheal pressure was equal to the ventilator pressure during a prolonged end-expiratory pause. Respiratory rate, tidal and minute volumes, and airway pressures above the endotracheal tube were measured using a Pitot type D-lite flow/airway pressure sensor connected at the y-piece[86].
Functional residual capacity was measured according to the method in Paper II.

Tracheal P/V-loops were analyzed during ongoing ventilation. Flow ($\dot{V}$), pressure (P) and volume (V) were obtained breath-by-breath during inspiration ($\dot{V}_{insp}$, P_{insp}, V_{insp}) and expiration ($\dot{V}_{exp}$, P_{exp}, V_{exp}) at identical volume levels. Since the inspiratory and expiratory resistances are practically identical on each isovolume level, the following equations were used for calculation of the dynostatic alveolar pressure (P_{dyn})[74]:

$R_{insp} = (P_{insp} - P_{alv})/ \dot{V}_{insp}$

$R_{exp} = (P_{exp} - P_{alv})/ \dot{V}_{exp}$

As it is assumed that $R_{insp} \cong R_{exp}$

$P_{alv} = (P_{insp} \times \dot{V}_{exp} - P_{exp} \times \dot{V}_{insp})/(\dot{V}_{exp} - \dot{V}_{insp})$

The volume-dependent compliances (VDC) at initial, mid and final part of the tidal volume (V_T) were then determined at 5-15%, 45-55% and 85-95% of the V_T from the dynostatic alveolar P/V-curve, using analysis of volume differences divided by pressure differences.
Volume-dependent airway resistance (VDR) between trachea and alveoli was calculated from the same parts of the breath as VDC, by analysis of tracheal and alveolar differences divided by the corresponding volume changes.

AIRWAY GAS ANALYSIS

We circumvented the problem of synchronization of flow and gas concentration measurements by using only the plateau value of end-tidal and inspiratory O_2 and CO_2 concentration output signals. Flow measurements were obtained from the ventilator, and oxygen and carbon dioxide were measured using side-stream paramagnetic analyzers with response times of < 480 and 360 ms and an accuracy of ± 2 and 0.3 vol% respectively (95% of full gain, manufacturers specifications) (Papers I,II, III). The response time is fast enough to detect even the first

end-tidal plateau value correctly after making a step change in F_IO_2, and permits higher respiratory rates. The gas analyzers were calibrated with a calibration gas, where the analyzers are automatically zeroed repeatedly to avoid baseline drift (Papers II, III).
Gas for breath-by-breath analysis of inspiratory and end-tidal concentrations was sampled at the y-piece. Gas for analysis of mixed expired concentrations was sampled from a 5 litre mixing box, with a fan (Papers I, II).

EXPERIMENTAL PROCEDURES

Paper I:

Lung model:

The basal ´FRC´of the lung model was 1.6 L, and was increased stepwise to 1.8, 2.1, 2.4, 2.6 and 2.9 L by addition of volume to the single alveolus. Each reference level of FRC was determined by five repeated measurements by injection of 50 mL of CO_2 into the lung model and measuring the resulting CO_2 concentration. The $\dot{V}CO_2 / \dot{V}O_2$ was set at 200/200 and 200/240 mL/min.
Ten to twenty measurements of FRC with the O_2/CO_2 flux FRC method were performed at each set level of FRC, totally 110 measurements.

Patients:

Five apnoea manoeuvres were performed at three PEEP levels. The initial (treatment) level of PEEP was 10-15 cmH_20, and then PEEP was reduced with ~7 cm H_2O. Finally PEEP was set back to the initial level for the final measurements. There was a time span of 2-4 min between each apnoea in order to regain sufficient steady state. FRC was calculated from the average of three consecutive measurements, and this resulted in three final FRC values after five apnoea manoeuvres.
Difference in FRC values before and after changing PEEP was compared to spirometrically obtained ΔEELV. When the PEEP level was reduced by 7 cmH_2O, the expiratory tidal volumes were registered until they returned to the level before the PEEP decrease.
The cumulative expiratory tidal volume difference between the expiratory tidal volume before decreasing the PEEP and the expiratory tidal volumes registered

after the decrease in PEEP level until the expiratory tidal volume had reached the same level as before the PEEP decrease. This was regarded as the reference ΔFRC between the two PEEP levels (Fig 11). The same procedure was performed to establish the reference ΔFRC when PEEP was increased again.

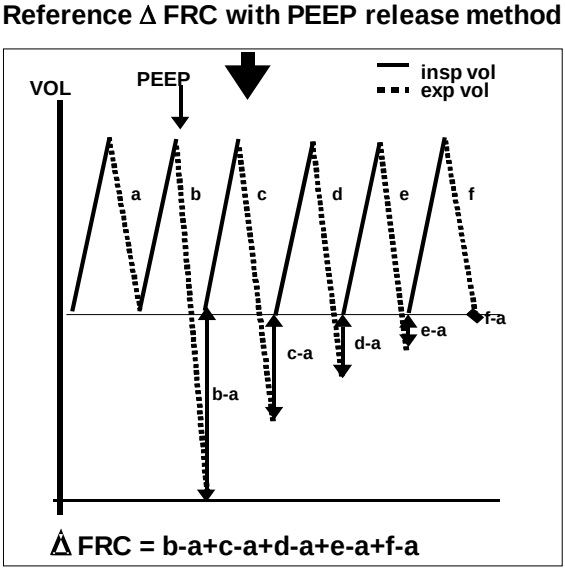

Figure 11: Schematic graph of expiratory tidal volume measurements before ('a' milliliters), and after release of PEEP ('b', 'c', 'd', 'e' and f' mL). The sum of the increase in expiratory volume above the expiratory volume before the PEEP release, until expiratory volume is approximately the same as before the PEEP release, is included. This sum was considered equal to the difference in FRC between the two PEEP levels. The increase in FRC when increasing the PEEP is calculated in a similar way. The sum of the decrease in expiratory volume after PEEP is increased, until the expiratory tidal volume is approximately the same as before the PEEP increase, and this represents the difference in FRC when increasing PEEP.

Paper II:

Lung model:

Three different lung volumes were used in the model, which was ventilated with a F_IO_2 of 0.4, 0.7, and 1.0. Nine different combinations of $\dot{V}CO_2$ and $\dot{V}O_2$, were used in combination with F_IO_2 step changes of 0.3, 0.2 and 0.1, to achieve a RQ of 0.7, 0.85 and 1.0.

Patients:

Twenty-eight patients were studied in volume control mode, with F_IO_2 0.3-0.6, inspiration 25%, end-inspiratory paus 10% and a respiratory frequency of 12-20/min. In 18 patients, FRC was measured during a stable PEEP level already set for clinical reasons. This was done by changing F_IO_2 step-wise up and then

back down by 0.1, 0.2 or 0.3 to achieve N_2 wash-out/wash-in measurements. After a stabilization period, the measurement was started with a step increase in F_IO_2 of 0.3 to induce a wash-out of N_2. After a new steady state was reached, as indicated by the concentration difference between inspiratory and end-tidal O_2 concentrations reaching the same level as before the start of the wash-out procedure, a step decrease of F_IO_2 of 0.3 to induce a wash-in of N_2 was performed. After steady state was reached again, the sequence was repeated with a step change of F_IO_2 of 0.2 and 0.1. The whole measurement sequence using step changes of F_IO_2 of 0.3, 0.2 and 0.1 was then repeated. In 17 patients (7 of whom were among the 18 patients above) FRC was measured by increasing and decreasing F_IO_2 by 0.1, at 2 PEEP levels, 5-8 cm H_2O apart.

Paper III

Lung model:

The paediatric model volumes were set to 130, 170, 220 and 320 mL. The model was randomly ventilated at respiratory rates of 20, 25 and 30/min with volume control (VC) or Pressure Regulated Volume Control (PSVC) with F_IO_2 of 0.4. The CO_2 flows were 40 or 70 mL/min and tidal volumes were 60 or 75 mL. FRC measurements by N_2 wash-in and wash-out were achieved by changing F_IO_2 by 0.1, as in Paper II. Measurements were repeated at each setting. Online FRC measurements were by then available via the beta version of Collect program (Datex-Ohmeda, Helsinki, Finland).
Values were accepted if the metabolic module reported stable values of gas exchange comparable to CO_2 flow delivered to model, and if values of wash-in and wash-out FRC did not differ >20%.

Patients:

Ten children undergoing surgery were ventilated, primarily in volume controlled (VCV) mode, at PEEP 3 cm H_2O. If time permitted, the mode was changed to pressure control (PCV) at identical tidal volume. Six children at the intensive care unit were ventilated in PSVC mode according to clinical conditions.
FRC measurements were then repeated at PEEP 7-8 cm H_2O after 10-20 minutes equilibration at the higher PEEP level. Measurements were duplicated at each setting.

Paper IV:

Animals:

In the porcine lung injury model, baseline ventilation (BV) constituted of volume control ventilation (VCV) at a PEEP level of 10 cmH_2O, inspiratory to expiratory ratio (I:E) 1:2, tidal volume (V_T) 10 mL/kg, and respiratory rate 20 breaths/min. During the three recruitment manoeuvres (RMs), the F_IO_2 was set to 0.5 and before each RM, derecruitment was first achieved by applying PEEP 0 cmH_2O (ZEEP) until PaO_2 was < 13 kPa. RMs then started after a ventilation period with PEEP 5 cmH_2O. During recovery periods, and for 15 minutes after the RMs, PEEP was set at 10 cmH_2O. Data were recorded continuously from baseline before, during and throughout the recovery period until 15 minutes after each RM. EELV was measured before each RM and after 15 minutes of recovery. Alveolar pressure-volume curves were used to determine changes in volume dependent compliance (VDC) and resistance (VDR) within each breath, including for the initial (Cini, Rini), middle (Cmid, Rmid) and final parts of the breath (Cfin, Rfin).

The RMs were performed in random order:

1. A high level pressure control manoeuvre (PCRM): PEEP 20 cmH_2O and peak pressure 20 cmH_2O above PEEP and I:E 1:1 applied for 30 s and then recovery at PEEP 10 cmH_2O. The manoeuvre was repeated three times.
2. A vital capacity manoeuvre (ViCM): PEEP 40 cmH_2O applied for 30 s and then 30 s recovery at PEEP 10 cmH_2O. The manoeuvre was repeated three times.
3. A slow, low-pressure manoeuvre (SLRM): PEEP 15 cmH_2O and prolonged end-inspiratory pauses performed for 7 s, twice per minute during 15 min in VCV.

STATISTICS

Paper I:

Correlation and agreement between techniques was determined using linear regression analysis and Bland and Altman representation.

Paper II:

Results are presented as mean ± SD. Comparisons between patient measurements with different step changes of F_IO_2 as well as duplicate measurements were performed using Bland and Altman analysis[87].

Paper III:

Bland & Altman analysis was used for assessment of agreement between volume of lung model FRC and calculated FRC, and between FRC during wash-in and wash-out in patients. Coefficient of variation was calculated from average values of FRC during wash-in and wash-out obtained from two consecutive measurements[88].

Paper IV:

Values are presented as mean ± SD. Analyses of variance for repeated measures were performed, followed by Fisher´s protected least significant difference test. Paired t test was used to evaluate changes between measuring points and differences between manoeuvres. Bonferroni corrections for multiple comparisons were performed. A p value of less than 0.05 was considered statistically significant.

RESULTS

Paper I

Lung Model

There was a good correlation ($y = 1.02x - 0.01$, $r^2 = 0.96$) and agreement between the FRC measured with the O_2/CO_2 flux method and reference FRC in the lung model, with a bias of 34 mL and limits of agreement (± 2SD) 160 and -230 mL, respectively (Fig. 12)

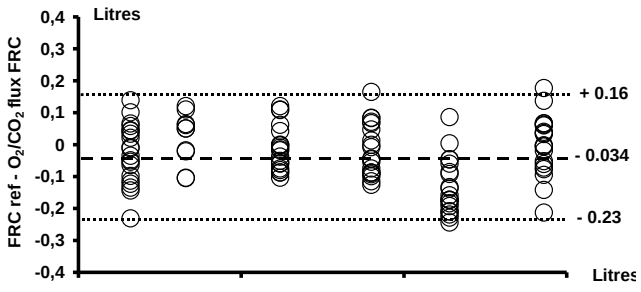

Figure 12: Bland & Altman plot, comparing FRC measured by O_2/CO_2 flux method (FRC_{flux}) and FRC in lung model (FRC_{ref}), showing minimal bias of 34 mL and limits of agreement (±2 SD) -230 and 160 mL, respectively.

Patients

FRC measured with the O_2/CO_2 flux FRC method decreased in a stepwise manner when PEEP was decreased with 7 cm H_2O, and increased stepwise when PEEP was increased to the initial level. The correlation was good between the decrease ($r^2 = 0.58$) and increase ($r^2=0.88$) in FRC volume measured with the O_2/CO_2 flux FRC method and the corresponding reference ΔFRC values measured from changes in expired tidal volume (Fig. 13).

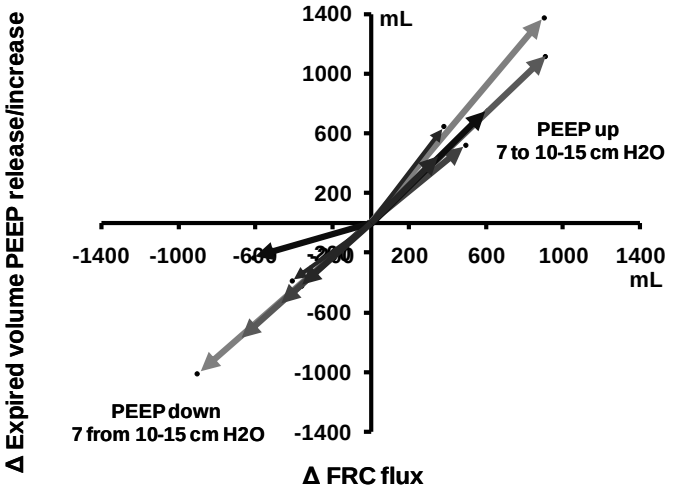

Figure 13: Correlation between changes in FRC, induced by a decrease (~7 cmH_20) or an increase (~7 cmH_20) in PEEP, measured by O_2/CO_2 flux method (FRC_{flux}) and corresponding values for FRC calculated from changes in expiratory tidal volumes (reference ΔFRC).

Paper II

Lung Model

Comparison between measured FRC using the NMBW algorithm and volumes of the lung model (1.8 L, 2.8 L and 3.8 L) showed good precision. Changes of ΔF_IO_2 of 0.1, 0.2, or 0.3 were 103 ± 5%, 101 ± 6%, or 102 ± 4%, respectively, and at F_IO_2 of 0.3-0.4, 0.7, and 1.0 the measured values were 100 ± 6%, 103 ± 8%, or 103 ± 7% of the reference FRC of the lung model.
When the RQ of the lung model was varied between 0.7 and 1.0 using the default RQ value of 0.85 for the NMBW algorithm, there was a small overestimation at a true RQ of 0.7 and 0.85, 116 ± 187 and 36 ± 192 mL, respectively. A true RQ of 1.0 showed a minimal underestimation of -19 ± 197 mL. These values corresponded to 4%, 1.3%, and -0.7% of the true FRC volume, respectively.
The difference between wash-out and wash-in measurements in the lung model using a step change in F_IO_2 of 0.1 was 14 ± 187 mL, corresponding to 0.5% of the true FRC volume (Fig. 14).

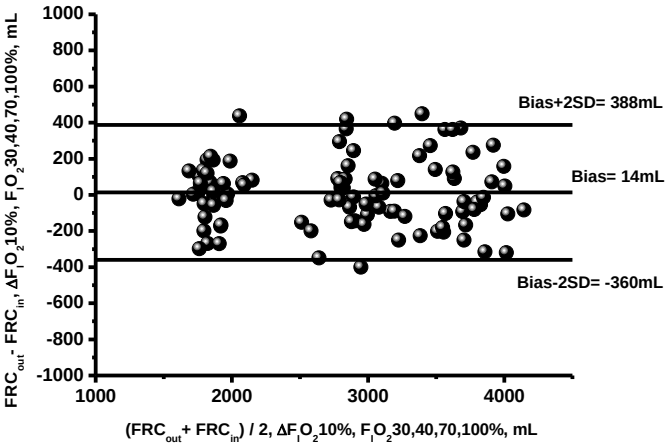

Figure 14: Comparison in lung model of measurements of FRC by N_2 wash-out and wash-in, using a step change of inspiratory fraction of oxygen (F_IO_2) of 0.1 from F_IO_2 of 0.3, 0.4, 0.7 and 1.0, shows the same precision.

Patients

Twenty-eight duplicate measurements were compared (FRC was represented by mean values of wash-out and wash-in) at F_IO_2 steps of 0.1, 0.2, 0.25, and 0.3, and showed a bias of -5 mL with a 95% confidence interval (CI) [-38, 29 mL].
In 17 patients, measurements of FRC were performed as duplicate wash-in/wash-out procedures at 2 PEEP levels (~ 7 cm H_2O difference) using step changes of F_IO_2 varying from 0.1 to 0.25. The bias of repeated measurements was -22 mL with a CI [-60, 16 mL] (Fig. 15). Comparing FRC measurements (mean of wash-in and wash-out) using an F_IO_2 step change of 0.1 or 0.3 showed a bias of -9 mL with limits of agreement ± 356 mL.
Comparing the wash-in with the wash-out procedures using a step F_IO_2 of 0.1 resulted in a bias of 149 mL with limits of agreement of 484 mL.

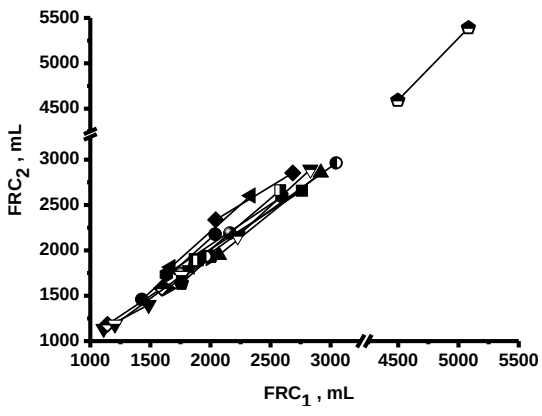

Figure 15: Regression between first (FRC_1) and second measurements (FRC_2) at two positive end-expiratory pressure (PEEP) levels in 17 patients. Functional residual capacity $FRC_2 = 1.04 \times FRC_1 - 71$, $r^2 = 0.99$.

Paper III

Lung Model

The difference between FRC measurements during wash-in and wash-out of nitrogen showed good correlation ($r^2 = 0.95$), and agreement was acceptable with a bias of 2 mL and an upper and lower limits of agreement of 32 and -29 mL (Fig. 16).
The difference between lung model volume and the mean of wash-out and wash-in values of FRC showed good correlation ($r^2 = 0.91$) with a bias of 9 mL, and upper and lower limits of agreement of 51 and -32 mL, respectively (Fig. 17).

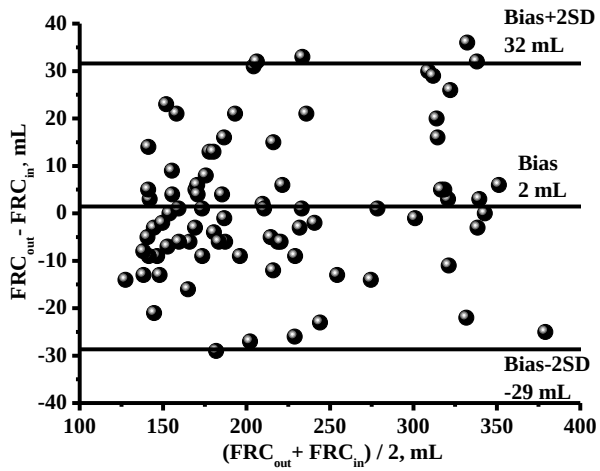

Figure 16: Assessment of agreement between 81 measurements of FRC in a pediatric lung model, during wash-out and wash-in at volume controlled and in pressure control modes at respiratory rates of 20, 25 and 30 min.

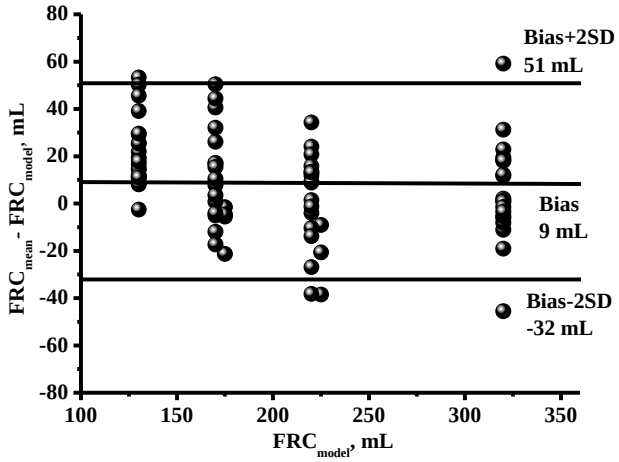

Figure 17: Assessment of bias and agreement for the mean of wash-out and wash-in FRC and volumes of pediatric lung model FRC of 130, 170, 220 and 320 mL.

Pediatric perioperative and intensive care FRC measurements

148 measurements fulfilled the criteria described in methods. Between wash-in and wash-out, a good correlation ($r^2 = 0.98$) was seen, with a bias of -0.02 mL, and upper and lower limits of agreement of 28 and -28 mL, respectively (Fig. 18).

Twenty-eight duplicate measurements were performed in 10 perioperative and 6 intensive care patients. Twelve patients were measured at two PEEP-levels. FRC was represented by mean value of wash-out and wash-in of the first and second measurement. Analyses showed good correlation ($r^2 = 0.99$) and agreement as well as a coefficient of variation of 2% (Fig. 19).

PEEP was increased in twelve patients. Four patients were measured both in VCV and PCV mode. FRC increased in all patients in response to an increase in PEEP (Fig. 20).

All measurements were re-run off-line using a default value for $\dot{V}CO_2$ derived from Brody´s equation. An assessment of agreement between the off-line and on-line measurements showed a bias of -33 mL and limits of agreement of 29 and -95 mL.

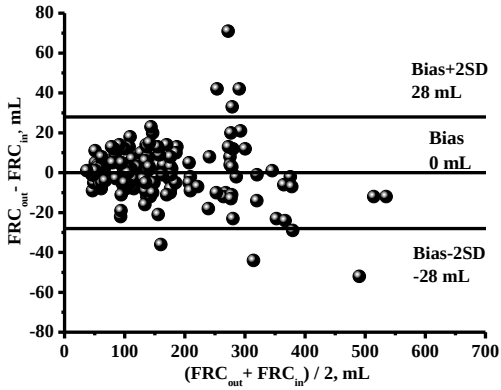

Figure 18: Assessment of agreement between 148 values of FRC calculated from wash-out and wash-in in 10 perioperative and six intensive care pediatric patients.

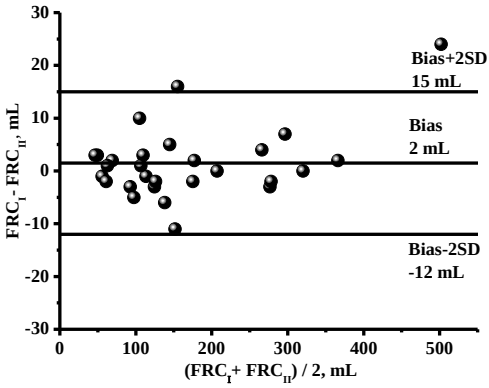

Figure 19: Assessment of agreement and repeatability between 28 duplicate measurements of FRC in 10 peri-operative and six intensive care measurements calculated as a mean value of wash-in and wash-out (12 patients measured at two PEEP levels).

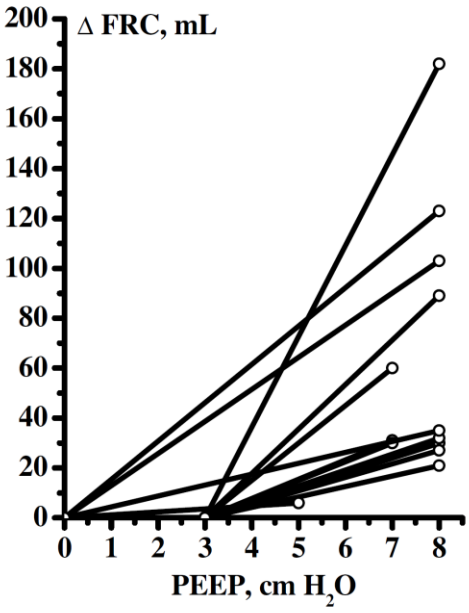

Figure 20: Relation between the increase in positive end-expiratory pressure (PEEP) and ΔFRC in 12 paediatric patients, with 4 patients measured both during volume control and pressure control ventilation.

Paper IV

Lung lavage was associated with large and significant decreases in volume dependent compliance (VDC) for the initial (Cini), the mid (Cmid) and final (Cfin) part of the tidal volume Fig. 21. In contrary, the resistance for the initial (Rini), the mid (Rmid) and final (Rfin) part did not change significantly.
Lung compliance recovered significantly after all three recruitment manoeuvres (RM), although particularly Cfin was still depressed compared to baseline values prior to lung lavage.
Lung resistance was significantly decreased ($p<0.001$) in all three RMs when comparing values before and 15 min after RM, although Rfin was higher immediately after PCRM.
EELV decreased significantly ($p<0.01$) after lung lavage, and increased significantly ($p<0.001$) for all three manoeuvres from before RM and 15 min after RM.

A responder to recruitment manoeuvre was defined as an increase of both Cini, Cmid and Cfin with > 25% following PCRM, ViCM and SLRM, and the responders were then 6/14, 5/14 and 9/14 animals respectively. Changes in VDC during a typical responder and non-responder are shown in Fig. 22 in which VDC is related to EELV. In the responder, successful RM was associated with both an increase in EELV and in VDC.

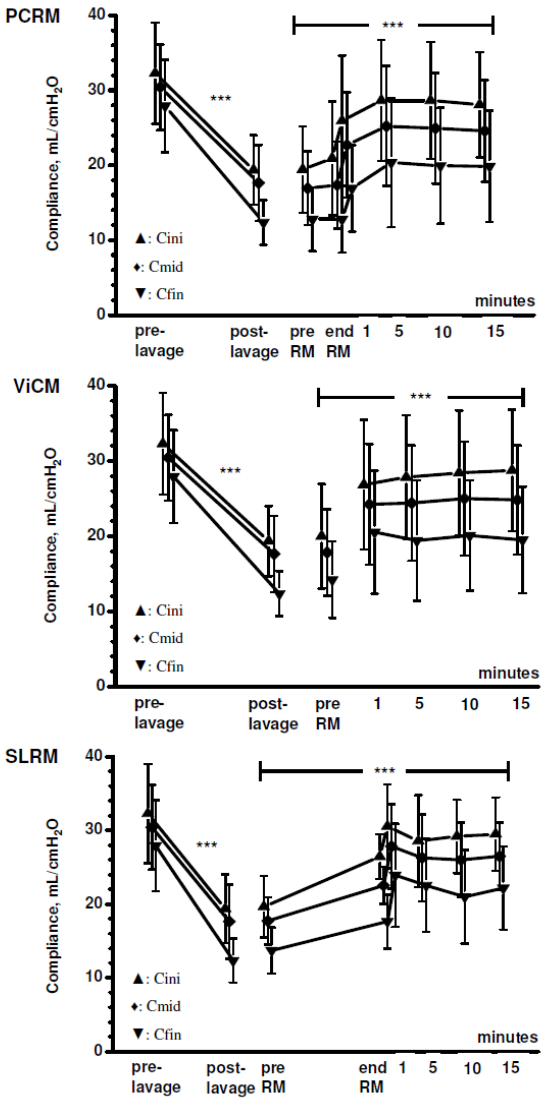

Figure 21: Temporal course of volume-dependent compliances during PCRM (pressure control recruitment manoeuvre - upper panel, during ViCM (vital capacity recruitment manoeuvre - middle panel), and during a slow RM - lower panel. Lung lavage was associated with a marked decreases in compliance for the initial (Cini), middle (Cmid) and final parts of the breath (Cfin). The different lung recruitment manoeuvres were associated with a significant recovery of volume dependent compliance although particularly Cfin was still depressed compared to pre lung lavage levels. *** p<0.001

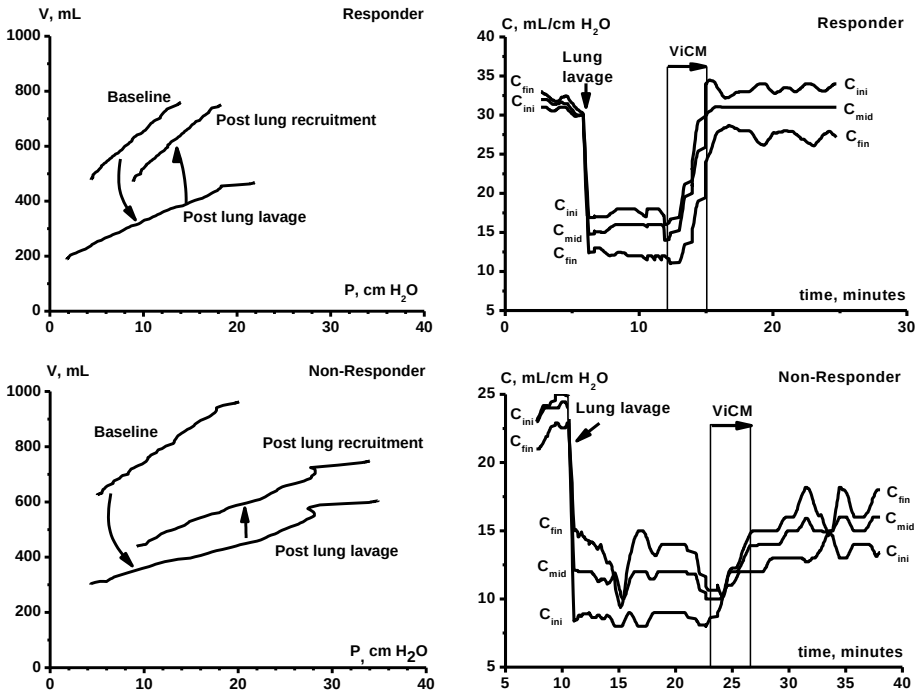

Figure 22: Alveolar pressure/volume curves (left panels) starting at end expiratory lung volume (EELV), measured using N_2 wash-in-wash-out technique and volume dependent compliances for an animal responding to a vital capacity recruitment manoeuvre (ViCM -upper panels) and for a non-responder (lower panels). Note the large decrease in lung volume (EELV) following lung lavage as well as the change in the pressure/volume slope. In the responder, lung recruitment was associated with an increase in lung volume (EELV) and a steeper P/V slope. In the non responder, lung recruitment was also associated with an increase in lung volume while the slope of the pressure /volume curve hardly changed and initial, middle and final part of tidal volume curve (Cini, Cmid and Cfin) remained depressed.

DISCUSSION

In this thesis, two new methods for bedside measurement of functional residual capacity/ expiratory lung volume (FRC/ EELV) are proposed. The first method is based on measurements of physiological fluxes of O_2 and CO_2 during a short apnoea (FRC_{flux}). The second method is a modified nitrogen wash-out/wash-in method where changes in inspiratory and end-tidal O_2 and CO_2 are measured breath-by-breath after a small step change in F_IO_2 for calculation of EELV (FRC_{N2}). The methods have been evaluated in a lung model and in ventilated adult patients (Papers I and II) and in small children and infants (Paper III). The strength of these methods is that they can be performed at the bedside using standard clinical monitoring equipment together with appropriate software for analysis. The FRC_{N2} method has been further developed and is considered the most useful clinically available method to measure FRC/EELV in critically ill patients[79,89]. In this thesis (Paper IV) the FRC_{N2} method was combined with a bedside technique for measurements of volume dependent compliance in an animal model of acute lung injury. It is proposed that combined use of these two methods could be helpful to define responders and non-responders to lung recruitment manoeuvres and PEEP changes and to be a valuable adjunct in the clinical management of ventilated critically ill patients.

METHODOLOGICAL CONSIDERATIONS

A number of physiological, technical and practical problems were encounter during the course of this project and are discussed below.

The original idea behind this project to develop clinically useful methods to measure EELV was actually based on the well known clinical observation in anaesthesia that patients with small FRC such as obese and pregnant patients desaturate rapidly during apnoea such as during induction of anaesthesia. This desaturation is even more pronounced in patients with already low FRC, and relatively high oxygen consumption. We first started to study this phenomenon in an oxygen-consuming lung model. First, oxygen uptake and carbon dioxide excretion were measured. Thereafter, the change in end-tidal CO_2 ($\Delta EtCO_2$) before and after a short apnoea was measured, and FRC_{CO2} was calculated as the amount of CO_2 during the apnoea (Vol $CO_{2apnoea}$)/$\Delta EtCO_2$. We were first encour-

aged by good correlation between calculated FRC_{CO2} and FRC measured in the lung model. Unfortunately, when the algorithm was tested in patients, measured lung volume, FRC_{CO2}, was too high. Returning to the lung model, the same procedure was performed again, but now by measuring end-tidal O_2 changes during a short apnoea. Again, the FRC_{O2} correlated well with FRC in lung model, but did not work properly in patients, although values now were more reasonable. Based earlier physiological knowledge that O_2 and CO_2 have totally different dissociation curves[17], we then assumed that this needed to be taken into consideration in the calculations for the FRC_{flux} method.

O_2 and CO_2 dissociation curves and fluxes of gases

Oxygen and carbon dioxide have different dissociation curves, body stores, and buffering capacity, although these stores play a limited role during a short apnoea. The apnoea causes an almost linear increase in alveolar CO_2 and decrease in O_2[90]. Because of the differences in behaviour of the gases, the fall in alveolar O_2 concentration is much greater than the rise in CO_2[91]. This is despite the fact that gas exchange over the alveolar membrane is close to equal with a respiratory quotient (RQ) near one.
A 10 seconds apnoea will not affect the outflow (oxygen uptake) from the alveoli, even if the alveolar oxygen tension falls. This is due to the O_2 dissociation curve, which is flat at O_2 tension levels present in the pulmonary capillaries and where the decrease in physically dissolved oxygen is negligible.
In contrast, the solubility of CO_2 in blood increases with the increase of CO_2 partial pressure during apnoea, and this leads to a decrease in inflow of CO_2 to the alveoli even though the metabolic production of CO_2 is constant[17]. Thus, the amount of CO_2 dissolved and retained in blood during the apnoea is dependent on the increase in alveolar and lung capillary CO_2 tension and cardiac output.

In search of a reference method for measuring FRC/EELV

After we obtained reproducible measurements with the O_2/CO_2 flux FRC method (FRC_{flux}), we needed to compare this to a reference method. A simple technique was to compare the changes in FRC_{flux}, during PEEP decrease with the corresponding changes in FRC (ΔFRC). We could do this by measuring the sum of the increase in expiratory volume above the expiratory volume before the PEEP release, until expiratory volume was about the same as before the PEEP release. The ΔFRC obtained by increasing PEEP was calculated by summing up the de-

crease in expiratory volume in a similar way. When comparing these two methods (FRC_{flux} and ΔFRC), a reasonably strong correlation was obtained.

Still, a reference method to use for comparison with the absolute lung volumes obtained with the FRC_{flux} method was needed. We did not have access to equipment for He and SF_6 analysis. Instead, a Douglas bag was used to collect expired gas from the ventilator following a change in F_IO_2 to achieve a wash-in or wash-out of nitrogen. Gas was analysed, and FRC/EELV calculated. Unfortunately, these measurements were not successful at first, when we observed measured FRC values of around 18 litres in pilot experiments in patients! These problems encouraged us to try to solve problems which had been previously described with the multiple breath wash-out techniques[59].

Breath-to-breath gas analysis (Papers II, III)

There are several problems which are encountered when using multiple breath wash-out techniques, including, for instance, with nitrogen, N_2. The conventional nitrogen multiple breath wash-out (NMBW) technique, where side stream gas analysis is delayed in relation to the direct main stream gas flow measurements, requires synchronization of gas flow and concentration measurements,. This has to be performed prior to the continuous integration of flow concerning direct or indirect N_2 concentration derived from O_2 and CO_2 measurements[46].
To avoid the synchronization problems, we focused on alveolar N_2 exchange calculated from inspiratory and end-tidal plateau gas concentrations of O_2 and CO_2. A basic assumption is that inhomogeneity in alveolar gas distribution, reflected in steeply increasing or decreasing end-expiratory plateaus, is constant throughout the measurement procedure. Another assumption is that cellular metabolism and gas exchange between lung capillary blood and alveoli are stable during the wash-out/wash-in procedure.

In adults, a wash-out or wash-in procedure takes normally less than 4 minutes to complete, and results in a brief and small change of alveolar O_2 concentration. In the setting of chronic obstructive pulmonary disease (COPD), however, the washout may take longer time due to large FRC and inhomogenous lung. These patients are usually excluded from evaluation studies and also from this study. We assume the deadspace for O_2 and CO_2 to be equal[92]. Theoretically, the difference in response time of the gas analysis equipment could result in the inspiratory and end-tidal O_2 concentration being a little too small or large, respectively, and not comparable to the corresponding CO_2 values. There could be an effect on the calculations of FRC if a stepwise change in F_IO_2 causes a change in

time constants of different parts of the lung. However, we saw no signs in the curve forms indicating such a time constant change, and a reasonable assumption was made that the lung compartment characteristics are identical before and after the wash-out and wash-in measurement procedure. Errors caused by differences in response time during a wash-in will be counterbalanced by the same errors during the following wash-out procedure.

Indirect calorimetry and high F_IO_2 (Papers II,III)

To calculate FRC, a step-change up and down of F_IO_2 of 0.1 for less than 4 minutes was used. In patients ventilated with 100% oxygen, a 0.1 step down and up was used. Since these patients have a low FRC, the wash-out/wash-in procedure had a very short duration. These patients also have a very high degree of lung shunt. The step change in F_IO_2 would not affect the lung capillary haemoglobin saturation, but only the plasma oxygen content, which has a marginal effect on arterial oxygen saturation. The decrease in arterial oxygen saturation is thus limited, both in degree and duration, and this should present no risk even for critically ill patients ventilated with up to 100% oxygen. Our method is based on determination of baseline O_2 consumption and CO_2 production by indirect calorimetry, which is imprecise at $F_IO_2 > 0.7$ and not possible for measurement at all at F_IO_2 of 1.0. This is explained by the fact that the inspiratory minute volume is calculated from the expiratory minute volume and inspiratory oxygen concentration, mixed expired oxygen and carbon dioxide concentrations, assuming no net exchange of nitrogen (Haldane transformation). When F_IO_2 is high, the concentration of nitrogen will decrease, and the imprecision of the inspiratory volume calculation increases. At 100% inspired oxygen, no nitrogen is present, and the calculation of inspiratory minute volume by this technique is not possible.
We have shown that setting a default RQ of 0.85 at these high oxygen levels did not affect measurement precision. This indicates that RQ has a negligible effect on precision of FRC measurements. Therefore, when F_IO_2 is more than 0.7, $\dot{V}CO_2$ is calculated from mixed expiratory CO_2 concentration and expiratory-volume, and then $\dot{V}O_2$ is calculated with a default value of RQ of 0.85.

N_2 solubility (Papers II,III)

In spite of N_2 having a very low solubility in blood and tissue, a certain amount of N_2 diffuses between blood and alveoli during a wash-out and wash-in procedure. A consequence of this is that a single wash-out procedure results in overes-

timation of FRC of around 5% in adults. There is a similar amount of underestimation when FRC is measured by a single wash-in procedure in adults. It has been proposed that when F_IO_2 is changed by 0.8, 40 mL/min of tissue N_2 is diff-using in or out of the alveoli[93]. No correction was made for tissue output or uptake of N_2 during wash-out and wash-in, as N_2 uptake andoutput will cancel each other during the calculation of the average of wash-out and wash-in.

Nitrogen wash-out/wash-in technique in small children and infants

It turned out to be very difficult to build a paediatric lung model that worked well. The main problem was that the relationship between the tidal volume and the FRC is close to 1:1. This causes great problems with mixing of the gases in the "alveolus" of the model, observed, for example, as uneven "bumpy" end-tidal carbon dioxide plateau levels. Finally, we used a small container with a powerful miniature fan inside. Changes in FRC were achieved by adding water.
A first paediatric pilot study was performed in twenty-five children peroperatively during cranio-facial surgery. A circle system with a large bellow was used. However, we found that the stepwise change in oxygen was not fast enough due to the large volume of the breathing system. The change in oxygen concentration in the breathing system, despite high fresh gas flows. This resulted in differences in FRC values obtained during wash-out compared to wash-in. The system was then changed to a Mapleson-D system, where the system volume was very low, and high fresh gas flows brought about non-rebreathing conditions.
Measurements were performed in small children and infants undergoing less extensive surgery, as well as ventilated children and infants in the ICU (Paper III). FRC/EELV was calculated as the average of the wash-out and wash-in measurements, and discarded if values differed more than 20%. This was analogous to thermodilution cardiac output measurements, where measurements differing by a certain amount from a perceived mean are rejected. Due to the precision of the measurement equipment, sensitivity analysis showed that FRC calculations may vary ± 10%. The 20% difference criteria was chosen based on allowance for a difference due to tissue uptake/output, and the assumption of a biological variation of FRC of 10%. And it has been proposed that FRC measurements may vary 20% in patients and still be useful[16]. In the lung model, relatively wide limits of agreement of measurements were seen. This may be explained by the fact that it was difficult to obtain absolutely stable end-tidal gas concentrations, even with a strong fan inside the model's ´alveolus´. This is in

contrast to patients, where no such variation in the CO_2 concentrations was seen, and the limits of agreement were narrower.
The calculation of breath-by-breath N_2 exchange, V_TN_2, is dependent on the precision of the measurement of carbon dioxide production ($\dot{V}CO_2$), FO_2, FCO_2 and tidal volumes. The calculation of alveolar tidal volumes is dependent on the precision of the volumetric capnometry, where $\dot{V}CO_2$ is calculated from the synchronized measurement of FCO_2 and flow. FCO_2 is sampled at a rate of 200 mL/min from the gas sampling port in the Pedi-lite (GE Healthcare, Madison, USA) used in the paediatric study. During the initial measurements it was noted that the flow of CO_2 in the lung-model was not sampled correctly by the metabolic module. This is explained by the fact that during the later part of expiration, sampling flow exceeds expiratory flow and fresh gas without CO_2 is being drawn from the y-piece. A spacer was added between the Pedi-lite and the y-piece to solve this problem. This has the effect of storing expired gas for gas sampling during the later part of expiration. In the lung model, the size of the spacer was adapted to achieve congruence between the delivered and the measured flow of CO_2. The spacer adds 1-2 mL to the technical deadspace, which is a disadvantage in very small patients. The patients in this study were mechanically ventilated, and the end-tidal CO_2 concentrations were well within the normal range.

The Brody formula for oxygen consumption in paediatric measurements

During FRC/EELV estimation in the paediatric patients, measurements are performed close to the specification limits of the Pedi-lite. We used the metabolic module for $\dot{V}CO_2$ measurements. Therefore, a correct $\dot{V}CO_2$ was difficult to estimate. The FRC that was calculated was subject to influence from the $\dot{V}CO_2$ estimation and the spacer used. To diminish the risk of totally inaccurate $\dot{V}CO_2$ measurements, a $\dot{V}CO_2$ value was only accepted if it was within ± 50% of the $\dot{V}CO_2$ value from the Brody formula for $\dot{V}O_2$ **(**$\dot{V}O_2 = 10 \times kg^{3/4}$**)** multiplied by a default RQ value of 0.85. Only one patient was excluded due to these criteria (Paper III). When FRC was calculated according to the Brody formula, the values were around 20 % higher, which could be explained by that the Brody formula is most valid for non-sedated mammals. This indicates that the FRC measurements may be performed with a default value for the $\dot{V}CO_2$ which is

based on body mass and Brody´s formula. The default value could be reduced by 10-30%[94,95] during sedation/anaesthesia/ hypothermia, and increased by about 10% during stress to minimize the effect on FRC calculations. This would avoid the need for a spacer or special capacity for the gas monitors metabolic measurements in the clinical setting.

The "first breath" conundrum

A dilemma for measurements of FRC by N_2 dilution techniques is the gas measurements during the first breath. When the step change starts for inspired fraction of oxygen, a gas concentration front is created in the inspiratory tubing. This gas front may be initially anywhere in the inspiratory tubing in relation to the gas sampling point at the y-piece at the start of the first inspiration after the step change. Since the value of F_IO_2 entered into the calculations is accumulated from the later part of the O_2 recording, potentially the major part of the inspired volume can have the composition of the gas mixture before the step change. This problem has also been discussed in earlier studies[59], and in one study[46] the volume of nitrogen that enters the lung during the first breath after the change in F_IO_2 was actually corrected for when calculating the total amount of nitrogen washed in or out.
The wash-out/wash-in volume of N_2 during the first breath is the largest tidal N_2 volume during a measurement, and this accentuates the effect of the heterogeneous composition of the first breath. In the paediatric lung, the wash-out has a very short time constant, and may be completed within 10 breaths due to the relation between the "high" tidal volume and FRC/EELV. The method we use, only analysing plateau values of oxygen and carbon dioxide, cannot identify the amount of nitrogen in the first breath. This limitation needs to be addressed in future development of paediatric FRC measurements, since this ´first breath conundrum´ probably is the most important factor in causing variations in measurements even in the paediatric lung model. To solve this problem it should be possible, using modern computerized ventilator software, to synchronize the change in F_IO_2 so that the gas front of the new F_IO_2 is placed at the y-piece when starting the ´first breath´ of the measurement.

Clinical perspectives

Bedside measurements of FRC/EELV

Concerning the importance of measuring FRC, it was noted a few years ago that relatively few studies have been devoted to development and refinement of techniques for bedside lung volume measurements in mechanically ventilated patients[16]. While some studies have begun to appear and address this, until now we have lacked clinically applicable methods for measuring FRC/EELV[79,89]. Previous methods, such as helium dilution, are mainly used in research, and these have the disadvantage that they require disconnection of the ventilator with the risk of alveolar derecruitment, which makes it patient-unfriendly in routine clinical use[89]. In this thesis, two methods for measurements of FRC/EELV have been developed: the FRC flux and the modified N_2 wash-in/wash-out technique. These two methods show strong agreement, as shown in Fig 23 (unpublished data).

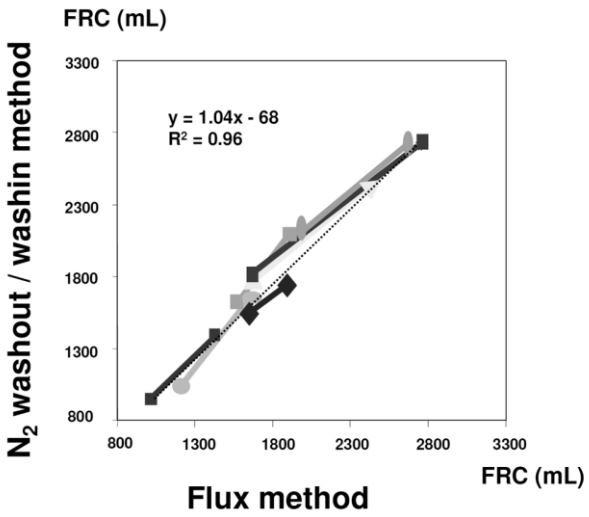

Figure 23: Seven ventilated patients were studied, each at two PEEP levels. There was good correlation (r^2 = 0.96) between O_2/CO_2 flux FRC (FRC_{flux}) compared to FRC obtained using nitrogen washout/washin (FRC_{N2}) (unpublished data).

The N_2 washin/washout technique has been more suitable for automatising, since it measures also slow compartments of the lung, which is not done with the FRC_{flux} method. The FRC_{N2} method is now the first measurement tool for FRC/EELV which has been incorporated into modern ventilators. After our studies, this technique has been validated using CT measurement of EELV in mechanically-ventilated patients, and strong correlation with quite narrow limits of

agreements as well as high reproducibilityhave been shown[22]. Feasibility studies measuring EELV in small children have also been performed[96]. Still, this technique needs to be validated concerning assisted ventilation. In the future we can expect other methods to become clinically available, including a technique based on wash-in/wash-out of oxygen using dedicated freestanding software (LUFU)[60,65].

Ventilator induced lung injury

It is now widely accepted that mechanical ventilation in itself may cause lung injury with pathophysiological effects on the lung parenchyma. Ventilatory strategies now include limitation of tidal volume to 6 ml /kg ideal body weight and/or airway plateau pressure below 30 cmH_2O as standard of care in ALI/ ARDS patients. These strategies reduce mortality in these patients[8]. Still, even these small tidal volumes may not be optimally "lung protective", and tidal hyperinflation may occur even with tidal volume and plateau pressures below these limits[97]. Indeed, a retrospective evaluation of the ARDSnet database has shown that further reduction in tidal volume would have improved outcome even in patients where plateau pressures below 30 cm H_2O were used[98]. Recently, Ranieri and co-workers showed that using tidal volumes of around 4 ml/kg body mass in patients with plateau pressures below 30 cm H_2O was associated with a significant reduction in inflammatory and morphological markers of ventilator induced lung injury (VILI)[99]. It was proposed that the respiratory acidosis caused by low tidal volume ventilation could be managed by extracorporeal carbon dioxide removal[99]. These studies show that it may be possible to further improve ventilation strategies to reduce VILI and improve outcome in ALI/ARDS. One problematic aspect of current ventilation strategies is that they treat all ALI/ARDS patients in the same way, or, that is that "one size fits all". This is in contrast to studies that show a large heterogenity in terms of lung mechanical properties such as in lung recruitability, or in other words the amount of collapsed lung tissue that can be opened by applying high airway inflation pressures.

The baby lung

Several years ago, Gattinoni and Pesenti[100] established the 'baby lung' concept and pointed out that the lungs of ALI/ARDS patients often are small rather than stiff. They meant that the reduction in lung compliance is due to the large decrease in functional residual capacity (FRC) rather than due to worsened mechanics of the aerated lung regions, that is, regions that may have nearly normal

intrinsic elasticity. The smaller the "baby lung", the greater risk will be for unsafe mechanical ventilation and VILI.
Similar problems are encountered in neonatal patients in whom the compliant chest wall results in a relatively larger degree of lung distension at all airway pressures[14]. Infants are even more susceptible to VILI than adults who have ALI/ARDS. There is also an association between mechanical ventilation in small infants and subsequent development of bronchopulmonary dysplasia[101]. VILI can begin to occur already after the first breaths after delivery if inappropriate ventilation is applied in terms of very large tidal volumes and no PEEP. In infants, it is crucial to match ventilatory strategy to the underlying patophysiology. It is possible that easy access to FRC measurements could be helpful to monitor infants with small FRC, where those with "baby baby lung" can receive individualised ventilation in terms of the most careful tidal volume and plateau pressure. Another cause of VILI in this patient group is atelecttrauma caused by surfactant depletion leading to alveolar collapse. Lung recruitment manoeuvres and high PEEP or high frequency ventilation could then be helpful to reduce VILI. At least during controlled mechanical ventilation in infants, FRC measurements could be used to monitor alveolar recruitment in terms of changes in lung volumes.

Stress and strain

A recent study[10] pointed out that lung stress and strain are the primary determinants of ventilator induced lung injury, and that the clinical equivalent of stress are transpulmonary pressure (airway pressure – pleural pressure) and the clinical equivalent of strain is the ratio of volume change (tidal volume, V_t) to the functional residual capacity (V_t /FRC). It was also shown that there are marked variations in the size of the lung and FRC in ALI/ARDS patients. Due to this FRC variability, or difference in size of the "baby lung", important lung strain variability may occur for the same applied tidal volume. These same authors showed that tidal volume referenced to ideal body weight (IBW) and airway plateau pressure are inadequate surrogates for lung stress and strain. It has been suggested that an ideal tidal volume should not be based on height and gender, as in the ARDSnet study[8], but instead it should be determined in relation to the size of the FRC[100]. Apart from measuring volume of gas in the lungs at rest, or FRC, measurements of transpulmonary pressure are also essential to evaluate the pathophysiology of the respiratory system[79].
The new bedside techniques for measurements of FRC/EELV will make it much easier to measure FRC/EELV in the clinical situations. It will now be possible to determine lung volumes repeatedly and serially during the course of respiratory failure and recovery both in adults and children/infants, and give the clinician a

rational for adjusting tidal volume according to the baby lung concept together with clinical measurements.

Monitoring alveolar recruitment

Limiting tidal volume and plateau pressure are parts of the concept of "lung protective ventilation"[9]. Another part of this concept is to prevent intratidal (within breath) collapse of lung areas using enough end-expiratory pressure to keep the lung open throughout the respiratory cycle. The optimal level of PEEP to use in ALI/ARDS patients is still not clear or generally accepted. Large randomised controlled studies on high versus low PEEP have failed to show a clear favourable outcome for patients with high PEEP levels[11-13]. This may be attributed to the fact that the disease is heterogenous with large variation between patients in lung recruitability[102]. When randomising this heterogenous patient group to high or low PEEP without knowledge of their potential recruitability, individuals with low recruitability would have limited or even negative effect of high PEEP-levels. Another explanation could be the inclusion of patients with elevated intra-abdominal and hence intrathoracic and esophageal pressure, where these patients need much higher PEEP levels to avoid collapse of their alveoli at end-expiration than those used in these studies[103]. It is obvious that the effect of PEEP-elevation depends on the lung mechanics of the individual patient. Successful recruitment of lung tissue results in improved oxygenation, increase of compliance, increase of end expiratory lung volume (EELV) and a decrease in end-tidal carbon dioxide tension. It should be noted that an increased EELV per se is not necessarily a result of lung recruitment, but can also be due to overinflation of already inflated alveoli. Compliance measurements may help to decide if an increase in EELV is due to recruitment or overinflation, since an increase in compliance following a recruitment manoeuvre can almost only be a result of alveolar recruitment. In this thesis, EELV measurements were combined with measurements of volume-dependent compliance (paper IV). The effect of lung recruitment manoeuvres as well as PEEP elevation on EELV could easily be determined, identifying responders and non-responders in terms of increases in EELV and changes lung compliance (paper IV). These two techniques are now incorporated in modern ventilators for clinical use and can lead to possible clinical benefits as illustrated in Fig 24 and 25. Clearly, a combination of different techniques are needed to assess lung mechanics along with the effect of changes in ventilation at the bedside, and this development constitutes an important part of modern respiratory management in patients with ALI/ARDS.

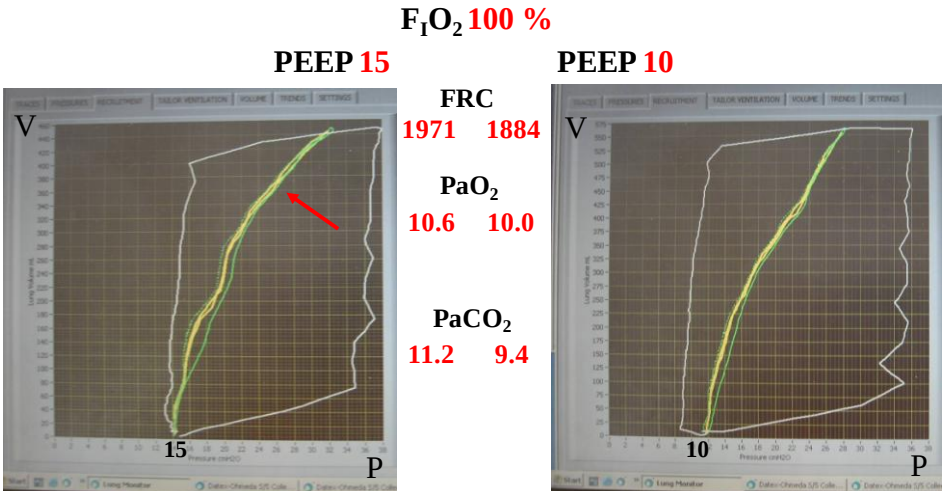

Figure 24: 80-year old man with pneumonia ventilated with F_IO_2 of 1.0 and with PEEP of 15 cm H_2O. PaO_2 was 10.6 kPa and $PaCO_2$ was 11.2 kPa. FRC was measured during wash-in/washout by changing F_IO_2 down to 0.9 and back to 1.0. Mean value of FRC was 1971 mL. The figures show the tracheal loop (white), and the dynamic (alveolar) pressure volume (P/V) curve (yellow/green). The P/V curve on left side, showed overdistension of the lung, see arrow. After decreasing PEEP to 10 cm H_2O, the P/V curve on right side, has straightened up and does not show overdistension any more. FRC and PaO_2 decreased marginally while $PaCO_2$ decreased to 9.4 kPa, probably due to decrease in alveolar dead-space. In summary, this patient probably only need PEEP 10 cmH_20 to keep the lung recruited and will have an increased risk of ventilator induced lung injury (VILI) if PEEP is increased further.

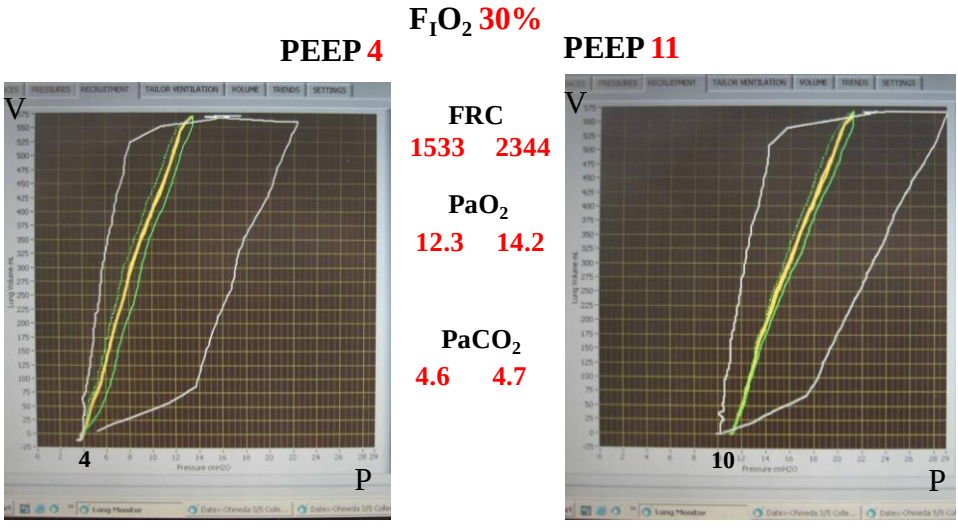

Figure 25: 71-year old man postoperatively mechanically ventilated with F_IO_2 of 0.1 and PEEP of 4 cm H_2O. When PEEP was raised to 11 cm H_2O the FRC increased with 800 mL and PaO_2 increased and $PaCO_2$ stayed at the same level. The P/V curves did not show overdistension. In summary, this patient tolerated a high PEEP without any sign of overdistension.

Conclusion

In this thesis, methodological work has been performed to develop clinical useful techniques to monitor functional residual capacity and end-expiratory lung volume in both adults and small children. With the modified N_2 wash-in/wash-out method which is included in a modern ventilator, is now possible in routine clinical practice to measure FRC/EELV at the bedside. Future studies and clinical experience will show whether this new technique, combined with other bedside techniques such as volume-dependent compliance, will be useful for the clinician to target ventilation for individual patients, both adults and small infants, to attenuate lung injury caused by mechanical ventilation.

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POPULÄRVETENSKAPLIG SAMMANFATTNING

Dödligheten är fortfarande hög, kring 40% för kritiskt sjuka patienter med akut lungsvikt, som kräver respiratorvård. Respiratorbehandling med övertrycksventilation är i sig livräddande men kan samtidigt skada lungorna och orsaka ventilatorinducerad lungskada (VILI). Lungskadan kan öka risken för sviktande funktion i andra organ i kroppen och leda till att patienten avlider. En minskning av dödligheten vid respiratorbehandling har åstadkommits genom att begränsa andetagsvolymen till 6 ml/kg kroppsvikt och ett högsta luftvägstryck till 30 cm H_2O. En ytterligare möjlighet att göra respiratorbehandlingen mer skonsam är att använda förhöjt positivt slutexpiratoriskt tryck (PEEP) för att undvika att instabila delar av lungorna upprepat öppnas och sluts under andetaget. Därmed minskas slitskador i lungvävnaden. Optimal PEEP-nivå är dock okänd och individuell för varje patient och varierar troligen under sjukdomsförloppet. Ett problem med respiratorbehandling är att vi hittills ofta behandlat alla patienter på ett likartat sätt trots att studier visat att patienter med akut lungsvikt har en mycket varierande sjukdomsbild. Helt klart har vi otillräckliga mätmetoder för att kunna skräddarsy respiratorbehandlingen för den enskilda patienten.

Vid akut lungsvikt hos vuxna vet man att man får en kraftig minskning av lungans vilovolym sk "baby lung". Studier har visat att andetagsvolymerna bör anpassas till lungans vilovolym för att minska risken för slitskador. Ju mindre "baby lung", ju större risk att skada lungan med respiratorbehandlingen. Nyfödda barn med akut lungsvikt har också en minskning av lungvolymen sk "baby baby lung". De är ännu mer känsliga än vuxna och respirator-behandlingen kan leda till lungskada (VILI) direkt efter födelsen om barnet ventileras på ett olämpligt sätt med stora andetagsvolymer och utan PEEP. Ett stort problem är att vi fram tills nu saknat kliniskt användbara metoder under pågående respiratorbehandling för att kunna mäta lungans vilovolym efter en normal utandning, sk funktionell residual kapacitet (FRC). Tekniker att mäta lungvolym har funnits sedan 1800-talet men kräver avancerad, otymplig och dyr mätutrustning och/eller tillförsel av icke kroppsegna spårgaser eller höga syrgashalter, som är skadliga för nyfödda barn. Vissa metoder kräver att man kopplar ifrån patienten från respiratorn under mätningarna med risker för patienten och ofta otillförlitliga resultat. Därför har man i stort sett endast mätt lungvolymer vid respiratorvård i forskningssammanhang. Målet med detta avhandlingsarbete har varit att utveckla enkla kliniska metoder för mätning av lungvolym hos vuxna och barn under pågående respiratorbehandling.

I första arbetet utvärderades möjligheten att mäta de från lungan utandande alveolära (från lungblåsorna) syrgas- och koldioxid- (O_2 CO_2) koncentrationerna, före och efter en kort andningspaus, apné, för att beräkna lungans vilovolym. Metoden utvärderades i lungmodell samt hos sex respiratorbehandlade patienter.

I andra arbetet modifierades en metod för mätning av lungans vilovolym genom stegvis ändring av koncentrationen av inandad syrgas och mätning av inandande

och utandande O_2- och CO_2- koncentrationer andetag för andetag. Även denna metod för beräkning av lungans vilovolym utvärderades i lungmodell och på 28 patienter vid olika respiratorinställningar vid ändring av inandad syrgas med 10-30%. I tredje arbetet utvärderades metodiken i lungmodell och på 16 barn, mellan 10 dagar och 5 år gamla. I arbete fyra användes en djurmodell med akut lungsvikt, där kombinerad mätning av förändringar av lungans vilovolym (FRC) och lungstyvhet (compliance) gjordes efter uppblåsning av lungorna med en sk lungrekryteringsmanöver.

I lungmodell uppvisade det uppmätta lungvolymvärdet mycket god överrensstämmelse jämfört lungmodellens volym. Hos patienterna mättes FRC-förändringar åstadkomna genom ökning eller sänkning av slutexpiratoriskt tryck som väl överensstämde med de uppmätta lungvolymförändringarna, uppmätta efter en kort andeningspaus. I lungmodellen resulterade metodiken där man beräknar lungvolymen efter en stegvis ändring av inandande syrgaskoncentration med 10 % för mätning av FRC_{N2}, en god överensstämmelse med jämfört med lungmodell. Noggrannheten var lika hög i mätningarna ända upp till en inandad syrgas koncentration på 100%. Upprepade mätningar visade god noggrannhet med bägge metoderna för mätning av lungans volym. Metoden där syrgaskoncentrationen i inspiratorisk gas ändrades utvärderas också i en lungmodell anpassad för små volymer (barnlungor) vilket också visade god resultat.

Försök i en lungsviktsmodell har visat på möjligheten att genom kombinerad mätning av förändringar av lungvolym (FRC) och lungstyvhet (compliance) kunna bedöma om en patient är ”svarare” eller ”inte svarare” genom att öppna upp lungorna när man gör en rekryteringsmanöver.

Sammanfattningsvis har arbete gjorts inom ramen för denna avhandling för att utveckla och utvärdera kliniskt användbara tekniker för mätning av lungvolym under pågående respiratorbehandling från nyfödda barn upptill vuxna. Båda metoderna för beräkning av lungvolymer (FRC_{flux} och FRC_{N2}) visade god tillförlitlighet hos vuxna och FRC_{N2} även på barn. FRC_{flux} och FRC_{N2} visade även god överensstämmelse sinsemellan. FRC_{N2} metoden som lämpar sig mest för automatisering är nu inbyggd in i moderna respiratorer. Metoden visar en god överensstämmelse med andra metoder för lungvolymsmätning, såsom datortomografi och har testats i ett flertal studier på vuxna och på små barn. Med vår modifierade kväveutsköljningsmetod är det nu möjligt i klinisk vardag, att patientnära mäta och följa förändringar i lungvolym (FRC) med användning av vanlig övervakningsutrustning. Fortsatta studier och kliniska erfarenheter får utvisa om denna nya teknik tillsammans med andra patientnära tekniker, som mäter lungstyvhet gör det möjligt för klinikern att skräddarsy respiratorinställningen utifrån den enskilda patientens förutsättningar och därmed kunna minska lungskada som orsakas av respiratorbehandling.