



UPPSALA  
UNIVERSITET

*Digital Comprehensive Summaries of Uppsala Dissertations  
from the Faculty of Medicine 1187*

# Patient safety in the Intensive Care Unit

*With special reference to Airway management and  
Nursing procedures*

JOAKIM ENGSTRÖM



ACTA  
UNIVERSITATIS  
UPSALIENSIS  
UPPSALA  
2016

ISSN 1651-6206  
ISBN 978-91-554-9493-3  
urn:nbn:se:uu:diva-275170

Dissertation presented at Uppsala University to be publicly examined in Enghoffsalen, Ingång 50, Akademiska sjukhuset, Sjukhusvägen, Uppsala, Friday, 22 April 2016 at 13:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish. Faculty examiner: Docent Peter Sackey (Department of Anesthesiology, Surgical Services and Intensive Care Medicine, Karolinska institutet).

### **Abstract**

Engström, J. 2016. Patient safety in the Intensive Care Unit. With special reference to Airway management and Nursing procedures. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1187. 72 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-554-9493-3.

The overall aim of the present thesis was to study aspects of patient safety in critically ill patients with special focus on airway management, respiratory complications and nursing procedures. Study I describes a method called pharyngeal oxygen administration during intubation in an experimental acute lung injury model. The study showed that pharyngeal oxygenation prevented or considerably increased the time to life-threatening hypoxemia at shunt fractions by at least up to 25% and that this technique could be implemented in airway algorithms for the intubation of hypoxemic patients. In study II, we investigated short-term disconnection of the expiratory circuit from the ventilator during filter exchange in critically ill patients. We demonstrated that when using pressure modes in the ventilator, there was no indication of any significant deterioration in the patient's lung function. A bench test suggests that this result is explained by auto-triggering with high inspiratory flows during the filter exchange, maintaining the airway pressure. Study III was a clinical observational study of critically ill patients in which adverse events were studied in connection with routine nursing procedures. We found that adverse events were common, not well documented, and potentially harmful, indicating that it is important to weigh the risks and benefits of routine nursing when caring for unstable, critically ill patients. In study IV, we conducted a retrospective database study in patients with pelvis fractures treated in the intensive care unit. We found that the incidence of respiratory failure was high, that the procedure involved in surgical stabilization affected the respiratory status in patients with lung contusion, and that the mortality was low and probably not influenced by the respiratory condition. In conclusion, the results obtained in the present thesis have increased our knowledge in important areas in the most severely ill patients and have underlined the need for improvements in the field of patient safety.

*Keywords:* intensive care unit, patient safety, nursing procedures, airway management

*Joakim Engström, Department of Surgical Sciences, Anaesthesiology and Intensive Care, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.*

© Joakim Engström 2016

ISSN 1651-6206

ISBN 978-91-554-9493-3

urn:nbn:se:uu:diva-275170 (<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-275170>)

*Till min familj*



# List of papers

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

- I Engström J, Hedenstierna G, Larsson A. Pharyngeal oxygen administration increases the time to serious desaturation at intubation in acute lung injury: an experimental study. *Critical Care*. 2010; 14(3):R93
- II Engström J, Reinius H, Fröjd C, Jonsson H, Hedenstierna G, Larsson A. Maintenance of airway pressure during filter exchange due to Auto-Trigging. *Respiratory Care*. 2014;59:1210-1217.
- III Engström J, Bruno E, Reinius H, Fröjd C, Jonsson H, Sannervik J, Larsson A. Non-reported adverse events during routine nursing procedures in critically ill patients are common: an observational study (Submitted).
- IV Engström J, Reinius H, Ström J, Frick Bergström M, Larsson I-M, Larsson A, Borg, T. Lung complications in intensive care treated patients with pelvis fractures - common but probably not fatal: a retrospective cohort study (Submitted).

Reprints were made after request of permission from the publishers.



# Contents

Abbreviations .....	9
Introduction .....	11
Patient safety .....	11
Medication errors .....	11
Patient safety in the intensive care unit .....	12
Endotracheal intubation: a patient safety issue .....	13
Disconnection from the endotracheal tube during mechanical ventilation .....	14
Pulmonary complications after major trauma .....	14
Study aims .....	16
Materials and methods .....	17
Paper I .....	17
Anesthesia, ventilation, instrumentation, and monitoring .....	17
Calculation of venous admixture and compliance of the respiratory system .....	17
Experimental protocol .....	19
Paper II .....	20
Clinical study .....	20
Study protocol .....	21
Bench study .....	22
Paper III .....	22
Study protocol .....	23
Survey of risk awareness of nursing procedures .....	25
Paper IV .....	25
Patient selection .....	25
AHF/ARDS .....	26
Statistical analysis .....	28
Paper I .....	28
Paper II .....	28
Paper III .....	28
Paper IV .....	29
Results .....	30
Paper I .....	30
Effects of lung lavage .....	30

Time to life-threatening hypoxemia .....	31
Relationship between shunt and time to life-threatening hypoxemia	31
Carbon dioxide and pH during apnea .....	32
Hemodynamics .....	32
Paper II .....	32
Clinical study .....	32
Bench study .....	36
Paper III .....	39
Clinical study .....	39
Survey of risk awareness of nursing procedures .....	42
Paper IV .....	43
AHF/ARDS .....	43
Analysis of the chest images .....	43
Incidence of AHF .....	45
Incidence of ARDS .....	45
Characteristics of patients with and without AHF/ARDS .....	46
Effect of the surgical stabilization procedure .....	46
Mortality .....	46
Discussion .....	49
Increased safety with pharyngeal oxygen administration -at least for some .....	49
Ventilator disconnection is always bad, is it not?! .....	52
Patient position change -time for a new perspective .....	53
If you survive to an ICU, there is a great chance to survive, if you are a trauma patient .....	56
Conclusion .....	59
Future perspectives .....	60
Acknowledgments .....	61
References .....	64



# Abbreviations

*AACN* – American Association of Critical-Care Nurses  
*AE* – Adverse event  
*AHF* – Acute hypoxic failure  
*AIS* – Abbreviated Injury Scale  
*ALI* – Acute lung injury  
*APS* – Acute Physiological Score  
*ARDS* – Acute respiratory distress syndrome  
*ASA* – American Society of Anesthesiologist  
*BE* – Base excess  
*bpm* – Beats per minute  
 $C_{aO_2}$  – Concentration of oxygen in arterial blood  
 $C_{c'O_2}$  – Concentration of oxygen in pulmonary end-capillary blood  
*CCRN* – Registered Critical Care Nurse  
*CICV* – Cannot intubate, cannot ventilate  
*CPOT* – Critical-care Pain Observation Tool  
 $C_{RS}$  – Compliance of the respiratory system  
*CT* – Computed tomography  
 $C_{vO_2}$  – Concentration of oxygen in mixed venous blood  
*Duration of MV* – Duration of mechanical ventilation  
*ECG* – Electrocardiography  
*EIP* – End-inspiratory plateau pressure  
*ETT* – Endotracheal tube  
 $FiO_2$  – Fraction of inspired oxygen  
*FRC* – Functional residual capacity  
*GCS* – Glasgow Coma Scale  
*HME* – Heat-moisture-exchanger  
*I:E ratio* – Inspiratory to expiratory time ratio  
*ICU* – Intensive care unit  
*ID* – Inner diameter  
*ISS* – Injury Severity Score  
*IV-lines* – Intravenous lines  
*MAP* – Mean arterial pressure  
*NAVA* – Neurally adjusted ventilatory assist  
*NISS* – New Injury Severity Score  
*NIV* – Non-invasive ventilation  
 $PaCO_2$  – Partial pressure of carbon dioxide in arterial blood  
 $PaO_2$  – Partial pressure of oxygen in arterial blood

$P_{AO_2}$  – Alveolar partial pressure of oxygen  
 $PaO_2/FiO_2$  – Partial pressure of oxygen in arterial blood/fraction of inspired oxygen  
 $P_{aw}$  – Pressure of the airway  
 $P_{ATM}$  – Atmospheric pressure  
 $PC-CMV$  – Pressure-controlled continuous mandatory ventilation  
 $PEEP$  – Positive end expiratory pressure  
 $P_{H_2O}$  – Vapor pressure  
 $P_{peak}$  – End-inspiratory peak pressure  
 $PRVC$  – Pressure regulated volume control  
 $PSV$  – Pressure support ventilation  
 $P_{VO_2}$  – Partial pressure of oxygen in mixed venous blood  
 $Q's$  – Blood flow through the shunt  
 $Qt$  – Cardiac output  
 $RASS$  – Richmond Agitation-sedation Scale  
 $Rbc$  – Red blood cell concentrate  
 $RQ$  – Respiratory coefficient  
 $SD$  – Standard deviation  
 $SAE$  – Serious adverse event  
 $SAO_2$  – Pulmonary end-capillary blood saturation  
 $SaO_2$  – Arterial blood oxygen saturation  
 $SAPS 3$  – Simplified Acute Physiology Score  
 $SOFA$  – Sequential Organ Failure Assessment Score  
 $SpO_2$  – Peripheral capillary oxygen saturation  
 $VAS$  – Visual Analog Scale  
 $VC-CMV$  – Volume-controlled continuous mandatory ventilation  
 $V_T$  – Tidal volume  
 $V_T/PBW$  – Tidal volume divided by predicted body weight

# Introduction

## Patient safety

According to the Institute of Medicine (IOM), a private, nonprofit institution that provides independent and objective analysis, patient safety is freedom from injuries or harm to patients from care that is intended to help them.

The first patient safety study in anesthesiology was published in 1929 by Hornabrook, in which the safety aspect of ethyl chloride was studied.<sup>1</sup> It was not until the mid-1970s that the yearly publication rate of patient safety studies exceeded 50 publications per year. The issue of patient safety has since gained

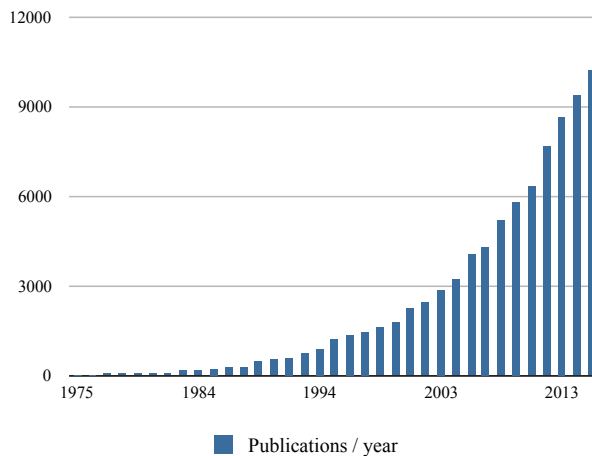


Figure 1. Publications per year in Pubmed with the search term “patient safety”

## Medication errors

There are numerous patient safety issues, and the most extensively studied one is probably errors in medication and drug administration.<sup>2-10</sup> One of the most important studies is the ground-breaking report “To Err Is Human: Building a Safer Health System” issued in 1999 by IOM in the U.S.<sup>11</sup> This report gained much attention, not only among researchers and health care workers but also from the public and the U.S. Government. Although controversy surrounds the mortality estimates,<sup>12,13</sup> IOM reported that medical errors causes 44,000 to 98,000 deaths and over 1 million injuries in the United States each year.

Almost half of patient safety issues in health care have been reported to be related to medication errors, and among errors leading to serious consequences for the patient, medication errors accounted for 75% of the cases.<sup>3</sup>

However, this means that at least half of the patient safety issues are not related to medication errors. In a study by Nuckols et al. in two U.S hospitals, medication errors accounted for 29% of patient safety incidents, and the rest were related to operations, procedures, falls, or diagnostics. In total, 9% of all patients had at least one safety incident during their hospitalization.<sup>14</sup>

However, in a study among 10 U.S hospitals between 2002 through 2007 with 2,341 reviewed patient records, the most common cause of incidents was medical procedures. In addition, of the 588 analyzed incidents, 43% required prolonged hospitalization, 3% caused permanent harm, 9% were life threatening, and 2% caused or contributed to the patient's death.<sup>4</sup> These findings are similar to those of another large multi center study among 26 hospitals in the U.S. reporting that among 92,547 reported incidents, 0.8% were life threatening and 0.4% contributed to the patients' death.<sup>15</sup>

## Patient safety in the intensive care unit

Although incidents and errors are problems of great concern in the whole health care system, some patients are more fragile than the average hospitalized patient. Critically ill patients constitute a small group of patients in need of the most advanced available health care. It is highly probable that in these patients, even small changes in, e.g., oxygenation or hemodynamics might induce a vicious cycle, deteriorating the patient's condition. Therefore, critical care presents significant patient safety challenges. Modern intensive care of severely critically ill patients is a fast paced, complex, and high risk environment. Many factors could potentially result in an increased rate of errors and adverse events that in the critically ill, may lead to fatal consequences.

Among 1,017 patients included in a Spanish study in 2012, 58% were affected by one or more incidents that in 4% caused permanent damage or damage that compromised patients' lives or contributed to their deaths.<sup>6</sup>

There are many different ways to categorize adverse events and the lack of consensus regarding the definition of an adverse event can sometimes be confusing. According to Wikipedia:

“An adverse effect is an undesired harmful effect resulting from a medication or other intervention such as surgery”

Some adverse event studies mainly focus on the incidence of medical complications, e.g., nosocomial infections, accidents during central venous puncture, peripheral thrombosis, pulmonary embolism, gastrointestinal bleeding, etc.<sup>16</sup> Other studies apply a wider approach when attempting to classify the adverse events as human/staff errors, medication/drug errors, and equipment

errors.<sup>17</sup> However, depending on the philosophical approach, almost all errors may be classified as human. For example, when a ventilator has an electrical malfunction, it is probably due to poor engineering or industrial design. The classification by Valetin and colleagues<sup>18</sup> is easier to understand and more applicable in daily intensive care. They classify adverse events depending on the type of event and in order of frequency in their study (lines, catheters, drains; medication; equipment; airways; and alarms). Equipment failures are a common denominator in many adverse event studies.<sup>10,17,18</sup> Welters and colleagues found that almost 30% of critical incidents were related to wrongful use of equipment and faulty equipment. My own clinical experience is in accordance with this finding, and this may show the complexity of caring for the critically ill patient. The care that we provide with the intention to treat patients, sometimes causes harm, and in rare cases, causes permanent harm or even death.

Even though the studies in this thesis are only small bits of the puzzle of knowledge of patient safety, our aim has been to shed light on patient safety issues that may seem trivial at first, but are probably of importance to the most severely ill patients.

## Endotracheal intubation: a patient safety issue

Endotracheal intubation, the placement of a flexible plastic tube into the trachea, in critically ill patients differs significantly from intubation prior to routine surgical procedures. In the operating room, airway management is typically undertaken in patients without any acute pulmonary disturbances and under controlled conditions, and the complication rate is therefore low. In contrast, endotracheal intubation in critically ill patients often requires emergency handling due to a state of compromised circulatory and pulmonary physiology.<sup>19</sup> This is often caused by low functional residual capacity (FRC)<sup>20</sup> in combination with pulmonary shunt and increased oxygen consumption, which contributes to a rapid development of hypoxemia during apnea.<sup>19,21,22</sup>

The endotracheal intubation procedure in critically ill patients has a high complication rate, and more than 20% of the intubations in the intensive care unit (ICU) are associated with severe complications such as hypoxemia, cardiovascular collapse, cardiac arrest, and even death.<sup>23</sup> The complication rate due to the difficulty of establishing a patent airway is correlated with both the numbers of laryngoscopic attempts and the time required for successful placement of the endotracheal tube. In more than 10% of the patients, more than two intubations attempts are made, and in 10% of the cases the intubation procedure takes more than 10 min.<sup>22-24</sup>

There are several methods used in clinical practice to extend the apneic time, with adequate oxygenation of the patient during the intubation procedure. Pre-oxygenation using a closed sealed mask is considered routine practice to prolong time to desaturation.<sup>25</sup> However, in more than 30% of the

patients intubated outside the operating room, this technique has very little effect.<sup>26</sup> Therefore, a number of different techniques have been proposed in the pre-oxygenation management of critically ill, e.g., non-invasive ventilation (NIV) with positive end-expiratory pressure (PEEP). Even though PEEP has been shown to be effective in improving oxygenation in both the pre-oxygenation period<sup>27,28</sup> and after intubation<sup>29</sup> there is a risk of rapid lung collapse within seconds after the removal of the positive end-expiratory pressure ventilation.<sup>30</sup>

An endotracheal tube (ETT) or tracheal cannula is a requirement to initiate invasive mechanical ventilation, which is often necessary to sustain acceptable respiratory function in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).<sup>31</sup> ARDS is defined as an acute inflammatory pulmonary condition with hypoxemia combined with bilateral lung infiltrates seen on computed tomography or x-ray. The cause is an inciting insult such as sepsis, major surgery, or trauma.<sup>32</sup> In contrast, mechanical ventilation can also cause harm to the lungs, e.g. ventilator-induced lung injury (VILI), and can thereby be a source of the development of ALI/ARDS.<sup>32,33</sup>

## Disconnection from the endotracheal tube during mechanical ventilation

Disconnection of the ETT from the ventilatory circuit during mechanical ventilation with PEEP expose ALI/ARDS patients to the risk of rapid development of atelectasis,<sup>34,35</sup> a risk that is even more substantial when endotracheal suctioning is performed.<sup>36</sup> It seems logical to assume that the number of disconnections should be kept to a minimum to minimize this risk, but this assumption has not yet been proven in clinical or experimental studies.

Numerous protective-ventilation strategies (ventilation with lower tidal volumes, lung recruitment maneuvers and PEEP) has been developed in an attempt to make mechanical ventilation less deleterious.<sup>33,37-40</sup> PEEP is often used to minimize cyclic alveolar collapse, shunt and improve arterial oxygenation.<sup>41</sup> One important factor regarding the improvement of oxygenation with PEEP is the reduction of formation of atelectasis.<sup>42</sup> Atelectasis can be caused by anaesthesia,<sup>20,43-45</sup> high concentration of inspired oxygen,<sup>46</sup> patient position<sup>47</sup> and obesity.<sup>48-50</sup> Atelectasis can result in several pathophysiological effects like decreased compliance,<sup>50-52</sup> impaired oxygenation,<sup>52,53</sup> increased pulmonary vascular resistance<sup>53,54</sup> and worsening of an already developed lung injury due to alveolar stress and strain.<sup>38</sup>

## Pulmonary complications after major trauma

Respiratory complications are common after major trauma<sup>55</sup> and one of the most serious forms is ARDS with an incidence of 12 - 25%.<sup>56,57</sup> Risk factors

for developing ARDS in trauma are Injury Severity Score (ISS), pulmonary contusions,<sup>58,59</sup> blunt injury mechanism, flail chest<sup>59</sup> and massive transfusion.<sup>59,60</sup> It is well recognized that pelvis fractures are associated with respiratory failure including ARDS.<sup>59,61,62</sup> Theoretically, respiratory failure could be aggravated by a “second hit” such as an inflammatory response induced by a surgical procedure. Therefore, surgical fixations in patients with pelvis fractures have sometimes been postponed in patients due to this reason. There are clear indications that early fixation reduces respiratory complications in patients with both femur- and pelvis fractures.<sup>63,64</sup> However, whether the surgical procedure per se affects the lungs negatively has to our knowledge, not been studied in patients with pelvis fractures. Moreover, although it is well known that intensive care treated patients with pelvis fractures often have respiratory complications, it has not been studied whether these specifically influence outcome.<sup>64</sup> Indeed, morbidity and mortality in ARDS caused by trauma is much lower than for other underlying conditions. Thus, mortality in a mixed ICU population with ARDS is 30 - 45%,<sup>32,56,65,66</sup> but in trauma patients with ARDS the mortality is 9 - 25%.<sup>57,67</sup> In addition, the incidence of severe respiratory complications in a European cohort of patients with pelvis fractures needing intensive care have not, what we are aware of, been studied.

# Study aims

The overall aim of this thesis was to assess patient safety among critically ill intensive care patients.

The specific aims of Papers I-IV were as follows:

- I. To evaluate whether pharyngeal oxygen administration would prevent or increase the time to life-threatening hypoxemia at intubation procedures during apnea in conditions with collapse-prone lungs with high shunt fractions.
- II. To assess whether the daily, routine exchange of the ventilator filters would lead to deterioration of oxygenation or compliance of the respiratory system in mechanically ventilated ICU patients. To further explore the mechanisms involved, we assessed in a bench test the airway pressure change proximal to the tip of the endotracheal tube after a simulated filter exchange.
- III. To examine whether adverse events caused by routine nursing procedures in patients with moderate to severe critical illness are common and whether these adverse events were registered in the medical chart or reported to supervisors.
- IV. To 1) assess the incidence of severe respiratory complications, i.e., ARDS or severe hypoxemic failure (AHF), in patients with pelvis fractures in our ICU, 2) whether the surgical intervention in these patients affects the pulmonary status of these patients, and 3) whether the lung complications influence mortality.



# Materials and methods

## Paper I

The study was approved by the Animal Research Ethics Committee at Uppsala University, Sweden, and the National Institute of Health guidelines for animal research were followed.

### Anesthesia, ventilation, instrumentation, and monitoring

Eight pigs (weighing 23 to 28 kg) were pre-medicated. After 5 to 10 min, the pig was placed supine on a table, the trachea was intubated, and the lungs were ventilated in a volume-control mode by a Servo-*i* ventilator (Maquet, Solna, Sweden) with tidal volume ( $V_T$ ) of 8 mL/kg, fraction of inspired oxygen ( $FiO_2$ ) of 0.5, and PEEP of 5 cm H<sub>2</sub>O. The rate was adjusted to keep end-tidal carbon dioxide tension at 5 to 6 kPa. Anesthesia was then maintained with ketamine 30 mg/kg/h and midazolam 0.1 mg/kg/h and with intermittent boluses of fentanyl. The depth of the anesthesia was tested intermittently with pain stimulation of the front toes. Ringer's acetate was infused intravenously to keep the pigs normovolemic. An arterial catheter was inserted into the right carotid artery for blood gas sampling and blood pressure monitoring, and a central venous catheter was inserted via the right external jugular vein. In addition, a pulmonary arterial catheter for measurement of cardiac output and pulmonary artery pressure was introduced via the right external jugular vein. A bladder catheter was inserted suprapubically to monitor urine production. Electrocardiographic monitoring was started, and peripheral capillary oxygen saturation ( $SpO_2$ ) was measured at the base of the tail.

### Calculation of venous admixture and compliance of the respiratory system

Venous admixture was calculated using the standard formula.<sup>68</sup> A  $FiO_2$  of 1.0 was used during sampling of blood gases; thus we regard our reported values for the venous admixture to be a very close estimate of the intrapulmonary shunt.<sup>68</sup>

The standard formula of venous admixture equation (shunt):

$$\frac{Q's}{Qt} = \frac{(C_{c'O_2} - C_{aO_2})}{(C_{c'O_2} - C_{vO_2})}$$

Where  $Q's$  is the blood flow through the shunt,  $Qt$  is the cardiac output (total blood flow),  $C_{c'O_2}$  is the concentration of oxygen in the pulmonary end-capillary blood in mL  $O_2/L$ ,  $C_{aO_2}$  is the concentration of oxygen in the arterial blood mL  $O_2/L$ , and  $C_{vO_2}$  is the concentration of oxygen in mixed venous blood mL  $O_2/L$ .

To calculate  $C_{c'O_2}$ , the  $P_{AO_2}$  needs to be calculated through the Alveolar air equation:

$$P_{AO_2} = (P_{ATM} - P_{H_2O}) - \frac{(PaCO_2)}{RQ}$$

Where  $P_{AO_2}$  is the alveolar partial pressure of oxygen in kPa,  $P_{ATM}$  is the atmospheric pressure in kPa,  $P_{H_2O}$  is the vapor pressure in kPa, the  $PaCO_2$  is the partial pressure of carbon dioxide in arterial blood in kPa, and  $RQ$  is the respiratory coefficient (0.8).

Then the  $C_{c'O_2}$  was calculated with:

$$C_{c'O_2} = \frac{P_{AO_2} * P_{H_2O}}{Hb(g/L) * 1.34}$$

Where 1.34 is the oxygen carrying capacity of one gram of hemoglobin (1.34 mL) in humans. Therefore, this is an approximation in other mammals (e.g., pigs).

$C_{aO_2}$  was calculated with:

$$C_{aO_2} = \frac{PaO_2 * P_{H_2O}}{\frac{Hb(g/L) * 1.34}{SaO_2}}$$

Where the  $PaO_2$  is the partial pressure of oxygen in arterial blood in kPa, and  $SaO_2$  is the arterial oxygen saturation in %.

$C_{vO_2}$  was calculated with:

$$C_{vO_2} = \frac{P_{VO_2} * P_{H_2O}}{\frac{Hb(g/L) * 1.34}{SAO_2}}$$

Where the  $P_{VO_2}$  is the partial pressure of oxygen in mixed venous blood in kPa,  $SAO_2$  is the saturation in the pulmonary end-capillary blood in %.

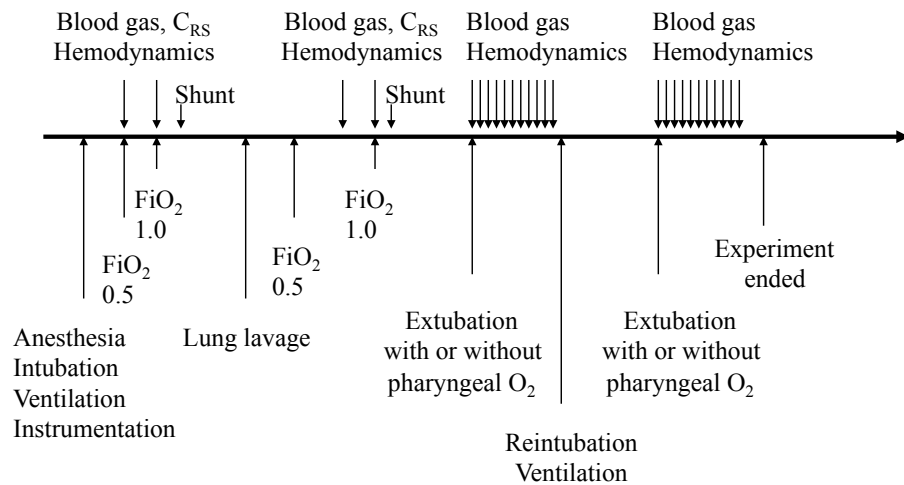
Compliance of the respiratory system ( $C_{RS}$ ) (mL/cm  $H_2O$ ) was calculated as:

$$C_{RS} = \frac{V_T}{(EIP - PEEP)}$$

Where  $T_V$  is the tidal volume in mL,  $EIP$  is the end-inspiratory plateau pressure in cm  $H_2O$  and  $PEEP$  is the positive end-expiratory pressure in cm  $H_2O$ . Both  $EIP$  and  $PEEP$  were measured after a 15-sec pause.

## Experimental protocol

An outline of the study is given in Figure 2. After the instrumentation, arterial blood was sampled for measurement of oxygen tension, carbon dioxide tension, pH, base excess (ABL 3, Radiometer, Copenhagen, Denmark), and oxygen hemoglobin saturation (OSM 3, Radiometer, Copenhagen, Denmark). Thereafter,  $FiO_2$  was changed to 1.0 and after a further 5 min, arterial and mixed venous blood gases were obtained for calculation of the pulmonary shunt. In addition,  $C_{RS}$ , cardiac output, heart rate, and systemic and pulmonary pressures were registered.

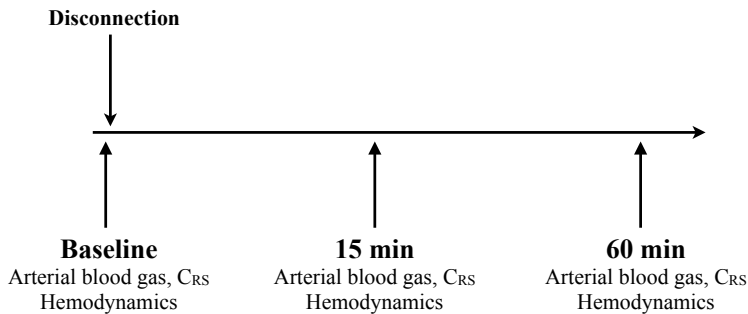


*Figure 2.* Outline of the experiment. The arrows above the horizontal line indicate measurements, whereas the arrows below the line indicate interventions. The two periods were randomized during which pharyngeal oxygen was or was not administered.  $C_{RS}$  compliance of the respiratory system,  $FiO_2$  fraction of inspired oxygen.

Thereafter, a collapse-prone lung was created by lung lavage. To achieve different levels of lung collapse and shunt fraction, the lungs were lavaged 3 to 10 times with 20 mL/kg isotonic saline at 38°C.  $FiO_2$  was reduced to 0.5, and the animals were left undisturbed for 30 min. If  $SpO_2$  decreased below 85%,  $FiO_2$  was increased to achieve a  $SpO_2$  above 85%. After 30 min, a new arterial blood gas sample was taken. A 12 French catheter was placed via one nostril (or if not possible, via the mouth) with its distal opening in the pharynx.  $FiO_2$  was changed to 1.0. After 5 min, arterial and mixed venous blood samples were taken for shunt calculation, and hemodynamic data and  $C_{RS}$  were registered. Fentanyl 0.2 mg and pancuronium 6 mg were given intravenously to assure that no attempts at spontaneous breathing occurred. In randomized order, either oxygen 10 L per min or no oxygen (no flow) was delivered via the pharyngeal catheter. The endotracheal tube was removed after the larynx had been localized by a laryngoscope, and the time was registered at which

the SpO<sub>2</sub> had fallen to 60%. After tracheal extubation, the laryngoscope was maintained in place.

Arterial blood gases were sampled before the tracheal extubation and then every min until and when SpO<sub>2</sub> was below 60% or until 10 min had elapsed. At similar time points, heart rate, and systemic and pulmonary pressures were registered. The trachea was again intubated; the lungs were ventilated with unchanged ventilator settings, except that the respiratory rate was increased in order to normalize end-tidal carbon dioxide. When end-tidal carbon dioxide was normalized, the lungs were ventilated for 5 min at the same rate as before the extubation. The trachea was again extubated, and the not-studied pre-oxygenation technique (without or with pharyngeal oxygen) was examined in the same way as described previously.



*Figure 3.* Outline of the study. The arrows above the horizontal line indicate interventions, whereas the arrows below the line indicate measurements.  $C_{RS}$  compliance of the respiratory system.

## Clinical study

The study was performed in Anesthesiology and Intensive Care, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden. The study was approved by the university ethics committee (ISRCTN.org registration IS-RCTN76631800). Informed consent was obtained from the subject's next of kin before inclusion.

Mechanically ventilated subjects were included consecutively if PaO<sub>2</sub>/FiO<sub>2</sub> ratio was ≤ 40 kPa, PEEP was ≥ 5 cm H<sub>2</sub>O, patient had an arterial cannula, patient was ≥ 18 years old, and the patient was not pregnant.

### Study protocol

The subjects were mechanically ventilated with pressure-regulated volume control (PRVC), pressure controlled ventilation, or pressure support ventilation using a Servo-*i* ventilator. Flow triggering was used and set at 1 L/min in all subjects. The inspiratory rise time was set at 5%. The ventilator tubing circuit set (A4VXXXXX, Vital Signs, Totowa, NJ, USA) had an inner diameter of 22 mm and was 275 cm in length (137.5 cm inspiratory and 137.5 cm expiratory limb). The size of the ETT (Portex Blue Line Sacett, Smiths Medical, Hythe, Kent, UK) or tracheostomy tube (Shiley Evac tracheostomy tube cuffed system, Covidien, Mansfield, OH, USA) was recorded, as well as whether a heat-moisture exchanger (HME, Pharma Systems, Knivsta, Sweden) or an active humidifier (RT430, Fisher & Paykel Healthcare, Auckland, New Zealand) was used.

Before the exchange of the high-efficiency particulate air filter (Servo Duo Gard, Maquet), placed between the expiratory limb of the ventilatory circuit and the ventilator, T<sub>V</sub>, breathing frequency, EIP, and PEEP were recorded (baseline). In the subjects with controlled ventilation without any subject-triggered breaths ( $n = 32$ ), Compliance of the respiratory system ( $C_{RS}$ ) was calculated as:

$$C_{RS} = \frac{V_T}{(EIP - PEEP)}$$

Both EIP and PEEP were measured after a prolonged pause of 10 sec. FiO<sub>2</sub>, arterial blood pressure, and pulse rate were recorded, and arterial blood was sampled for determination of PaO<sub>2</sub>, PaCO<sub>2</sub>, pH, and base excess (ABL 800 Flex).

The subject remained connected to the ventilator during the whole filter exchange procedure. The expiratory tubing was disconnected from the old filter, which was then removed from the ventilator inlet and exchanged, and the expiratory tubing was reconnected to the new filter. Measurements were repeated 15 and 60 min after the filter exchange. In addition, the duration of the exchange procedure was recorded. Finally, in four subjects, airway pressure ( $P_{aw}$ ) was measured in the Y-piece connected to the ETT and 1 cm below the ETT tip via a 15-cm, 16 gauge catheter (Arrow, Limerick, PA, USA). Endotracheal disconnection and suctioning were not performed in any subject for at least 4 hr before study inclusion. No changes were made in subject position or ventilator settings during the study protocol.

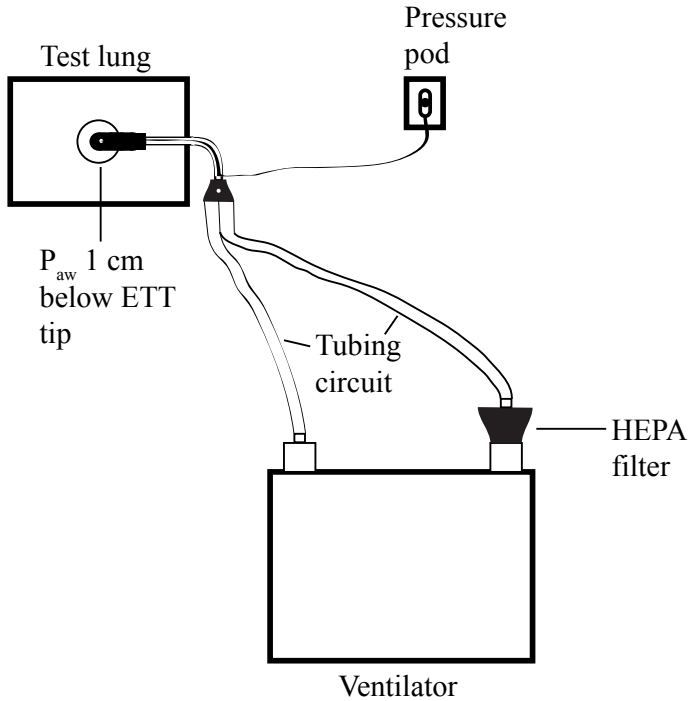
## Bench study

The “tracheal” airway pressure decrease was measured in a lung model (Accu Lung precision test lung, Fluke Biomedical, Everett, WA, USA).

The test lung was set at compliance values 10 or 20 mL/cm H<sub>2</sub>O, resistance 5 cm H<sub>2</sub>O/L/sec (the resistance setting was chosen to avoid inadvertent auto-PEEP), and was connected through an inner diameter 6 or 8 mm ETT (Portex Blue Line Sacett) and a 275-cm, inner diameter 22-mm tubing circuit (A4VXXXXXX, the same as used in the clinic) to a Servo-*i* ventilator set at either pressure controlled ventilation (EIP 25 cm H<sub>2</sub>O, 10 cm H<sub>2</sub>O PEEP, or volume-controlled ventilation with the same EIP and PEEP as during pressure controlled ventilation. The ratio of inspiratory time to expiratory time (I:E ratio) was 1:2 and the respiratory rate 15 or 25/min. The inspiratory rise time was set at 5% (similar to subject values),  $P_{aw}$  was measured 1 cm below the ETT tip in the test lung via a 15-cm, 16 gauge catheter (Arrow). At each of the above combinations, the expiratory circuit was disconnected from the ventilator during 2, 3, 4, 5, 6, and 10 sec to simulate filter exchange. The filter was disconnected from the tubing. Flow trigger set at 1 L/min and pressure trigger set at -20 cm H<sub>2</sub>O were used at every step. In addition, the suctioning support function was activated at the end of each sequence. During all the procedures, inspiratory flow (obtained from the ventilator) and tracheal pressure were registered.

## Paper III

The study was approved by the local ethics committee at Uppsala University, Uppsala, Sweden and the study was registered at ISRCTN.org number, ISRCTN73736539. Informed consent was obtained from the patient’s next of kin before inclusion. The study was conducted in a nine-bed mixed ICU in a tertiary referral university hospital in Sweden with 940 beds. The unit is staffed daily by three intensivists, two trainees, and six registered critical care nurses (CCRN). The nurse/patient ratio is 1:2. The unit treats 980 patients per year, with a mean length of stay of 3 days and an ICU mortality of 7%. There were no written routines regarding patient position change procedures in the studied ICU. However, patients are routinely submitted to position change every 2 hr. When performing endotracheal suctioning, there was a written routine specifying the use of a maximum negative suctioning pressure of 20 kPa and the recommendation to use suction support<sup>©</sup>, Servo-*i* ventilator before suctioning (30% increase in inspired oxygen concentration within 120 sec before and for 60 sec after suctioning<sup>69</sup>). The size of the suctioning catheter should be less than 50% of the diameter of the endotracheal tube and that suctioning should be performed with 5-sec cycles and no longer than 20 to 30 sec in total duration. There was no validated tool used to assess pain in non-verbal



*Figure 4.* Experimental setup of the bench test. The high-efficiency particulate air filter was placed in the expiratory limb of ventilator.  $P_{aw}$  airway pressure, *ETT* endotracheal tube.

patients in addition to the visual analog scale (VAS). However, the Richmond Agitation-sedation Scale (RASS) was used to evaluate the sedation level.

In this study, we consecutively included mechanically ventilated patients with  $\text{PaO}_2/\text{FiO}_2$  ratio  $< 40$  kPa with  $\text{PEEP} \geq 6$  cm  $\text{H}_2\text{O}$  combined with need of vasopressor support (noradrenaline  $\geq 0.05$  mcg/kg/min). Exclusion criteria were 1. Decision to withdraw life-support within 24 hr, 2. Glasgow Coma Scale (GCS) = 3, 3. Less than 18 years of age, 4. Pregnancy.

## Study protocol

The observational period started at 06.00 AM and continued for 12 hr. The observer was always a CCRN with at least 5 years of ICU experience and did not participate in the regular care during the observation. Before the start of the observation, baseline parameters were recorded: respiratory:  $V_T$ , respiratory rate, PEEP, end-inspiratory peak pressure (P<sub>peak</sub>),  $\text{FiO}_2$  and  $\text{SpO}_2$ ; circulatory: pulse and mean arterial pressure (MAP). Awareness was assessed with

RASS.<sup>70</sup> All ongoing drug infusions and doses were registered. The observer was fully familiar with the sedation scale.

During the 12-hr period, the observer recorded all physiological variables/parameters just before the start and continuously during all procedures on a sheet dedicated to the study. All parameters were also continuously sampled from an ICU monitoring system during the whole observational period (Dräger Infinity Delta, Dräger, Lübeck, Germany) and printed on paper after the observational period ended (data sampling rate 1/min). If additional procedures were started before a previously started procedure had ended, we only registered the first procedure most likely to have generated the adverse event. However, a single procedure could generate multiple adverse events. Spontaneous changes in physiological parameters were also recorded to reevaluate baseline threshold values but were not registered as adverse events. Duration of the adverse events and any measure to reduce the effect of the adverse events were also recorded. The observer also recorded all pharmacological therapies and changes in those therapies given during the study period. The observer did not record any information about the staff caring for the patient. All data recorded by the observer were compared with the paper copies from the ICU monitoring system.

The observer did not interact or interfere with the caregivers, and thus, whether any adverse event should be documented in the medical chart or reported to supervisors was up to the discretion of the nursing staff.

*An adverse event (AE) was defined as one of the following:*

- Heart rate change  $\pm 15$  beats/min (bpm).
- Change in MAP  $\pm 5$  mmHg.
- Desaturation  $-5\%$  in SpO<sub>2</sub>.
- Respiratory rate change  $\pm 5$ /min.
- Awareness: RASS +1.
- Ventilatory distress: ventilator asynchrony (coughing, frequently breathing against the ventilator).

*A serious adverse (SAE) event was defined as one of the following:<sup>71</sup>*

- Tachycardia: heart rate  $\geq 110$  bpm if  $< 100$  bpm before the procedure.
- Bradycardia: heart rate  $\leq 60$  bpm if  $> 70$  bpm before.
- Hypertension: MAP  $\geq 110$  mmHg if  $< 100$  mmHg before.
- Hypotension: MAP  $\leq 60$  mmHg if  $> 70$  mmHg before.
- Desaturation: SpO<sub>2</sub>  $\leq 90\%$  if  $> 92\%$  before.
- Bradypnea: respiratory rate  $\leq 10$  /min if  $> 10$  /min before.
- Ventilatory distress: severe ventilator asynchrony (nonstop coughing, not possible to mechanically ventilate and/or tachypnea (respiratory rate  $\geq 35$  /min if it was  $< 35$  /min).
- Serious arrhythmia
- Cardiac arrest



Demographical/medical data were prospectively recorded. Age, gender, admission type, Simplified Acute Physiology Score (SAPS 3), Sequential Organ Failure Assessment Score (SOFA), duration of mechanical ventilation, ICU/hospital stay, ICU/hospital mortality, 60-day mortality, degree of ARDS and arterial blood gas values (PaO<sub>2</sub>, PaCO<sub>2</sub>, pH, and base excess (ABL 800 Flex, Radiometer, Copenhagen, Denmark)).

## Survey of risk awareness of nursing procedures

To assess the nursing personnel's awareness of potential risks during routine nursing procedures, we conducted an electronic survey among the CCRNs working in the ICU where the observations had taken place. The survey contained 16 questions and was sent to all nurses of the ICU after all patients were included into the study. Non-responders were sent a reminder.

## Paper IV

The study was approved by the local ethics committee at Uppsala University, Uppsala, Sweden, and the study was registered at ISRCTN.org number, ISRCTN10335587. Data were obtained from a cohort of 669 patients admitted to the Uppsala University Hospital scheduled for surgical stabilization of pelvis ring and/or acetabulum fractures. In addition to the patients in the local region of the Uppsala University Hospital, 30 additional hospitals referred patients after providing primary care.

## Patient selection

All patients in the database cohort, admitted to the general ICU at Uppsala University Hospital, between 2007 and 2014 for intensive care treatment/monitoring were prospectively included.

Exclusion criteria were: 1. Not admitted to the ICU. 2. No arterial line present during the ICU stay, 3. Younger than 18 years of age, 4. Pregnancy. One hundred and twelve patients were eligible for inclusion in the study (Figure 5).

Demographical/medical data, ICU/hospital stay, ICU/hospital mortality, and 60-day mortality were retrospectively recorded from the database. From the medical charts, data were collected, and the following scores were calculated: SAPS 3, SOFA, Injury Severity Score (ISS), New Injury Severity Score (NISS), Abbreviated Injury Scale (AIS), and GCS. In addition, from similar sources, we registered the incidence of thoracic injury, time between injury and surgical intervention, duration of surgery and perioperative blood

**669 Available trauma patients**

Pelvis fracture database cohort  
between 2003 - 2014

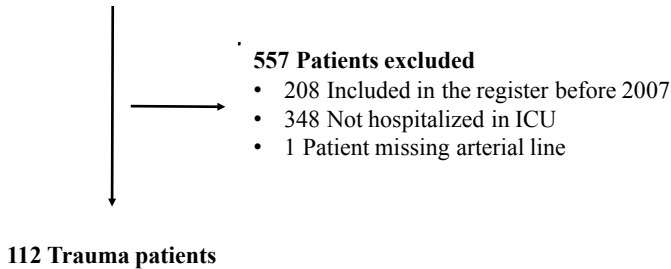


Figure 5. Patients included from the Pelvis fracture database cohort. *ICU* intensive care unit.

loss. The number of transfusions of red blood cells, fresh frozen plasma, and platelets was recorded from the ICU and anesthesia charts as well as the amount of synthetic colloids and crystalloids administered between date of injury until discharge from ICU. Moreover, ventilator data (i.e.,  $T_V$ , airway pressures, and  $FiO_2$  and arterial blood gas values ( $PaO_2$ ,  $PaCO_2$ , pH, and base excess (ABL 800 Flex)) were collected from the medical charts. In all patients, low-molecular weight heparin was administered subcutaneously as prophylaxis against venous thrombosis for a minimum of 10 days after surgery, and prolonged for patients not mobilized by that time. Systemic prophylactic antibiotics were given perioperative for a minimum of 24 hr.

## AHF/ARDS

The Berlin definition of ARDS was used in this study.<sup>72</sup> AHF was defined according to the ARDS definition without the radiologic criterion. All patients' radiological chest images (both standard radiograms and computed tomography (CT)) were downloaded from the hospital radiological system, Vue Motion<sup>®</sup> 12.0 (Carestream Health Inc., Rochester, NY, US). Two chest radiological examinations were selected for analysis, one pre- and one post-operative. The chest images used for the analysis were obtained within 2 days before and within 2 days after surgery, respectively. Two  $PaO_2/FiO_2$  ratios were used; the lowest values within  $\pm 12$  hr from the time point when the chest images were obtained. If no chest radiological examination has been performed, the two  $PaO_2/FiO_2$  ratios used in the calculation of AHF were the lowest values at  $48 \pm 12$  hr before and  $48 \pm 12$  hr after surgery, respectively. Single outlying  $PaO_2/FiO_2$  ratios values were excluded. Two experienced consultant intensivists analyzed independently all radiological chest images to determine whether the radiological criteria of ARDS were fulfilled. For the

images where there was a disagreement, the image was were reexamined in order to achieve a consensus.

# Statistical analysis

## Paper I

To obtain a  $P$  value of 0.05 and a power of 0.8 for the primary outcome variable, time to life-threatening hypoxemia ( $\text{SpO}_2 < 60\%$ ), eight animals were considered sufficient. For analyses of the differences between the pre-oxygenation techniques, Wilcoxon signed-rank test was used. Linear regression was used to analyze the relation between time to life-threatening hypoxemia and shunt fraction. The data are reported as medians with interquartile ranges unless otherwise indicated.

For the statistical analyses, the Sigmapstat statistical program (Systat, Software Inc, Point Richmond, CA, USA) was used.  $P < 0.05$  was considered as statistically significant.

## Paper II

The primary outcome variables were changes in  $\text{PaO}_2$ . A power analysis indicated that for a clinically important decrease in  $\text{PaO}_2$  ( $1 \pm 2$  kPa [mean  $\pm$  standard deviation (SD)]) with a  $P < 0.05$  and a power of 0.95, 32 subjects would be needed. We therefore enrolled 40 subjects in this study. The data were analyzed by one-way analysis of variance. The data from the bench test were analyzed with a t-test.

For the statistical analyses, the Prism 6.0 statistical program (GraphPad Software, La Jolla, CA, USA) was used.  $P < 0.05$  was considered a priori as statistically significant.

## Paper III

The primary outcome variable was the incidence of AE and SAE. We also analyzed the number of AEs and SAEs per procedure as well as the number of such events documented in the medical chart or reported to supervisors. For the statistical analyses, the SPSS 23.0 for Windows/Mac OS X statistical program (IBM Corp., Armonk, NY, USA) was used. All values are mean  $\pm$  SD if not otherwise stated.

## Paper IV

For the statistical analyses, the SPSS 23.0 for Windows/Mac OS X statistical program was used. One-way ANOVA with a post hoc test (Tukey) was used for the analysis of the differences among patients with and without AHF and ARDS. An independent t-test was used for the analysis of the difference among patients with pre-operative normal lung status who developed AHF/ARDS in relation to the surgical procedure and patients with AHF/ARDS who normalized their lung condition.  $P < 0.05$  was considered a priori as statistically significant. All values are mean  $\pm$  SD.

# Results

## Paper I

### Effects of lung lavage

The  $\text{PaO}_2$  on  $\text{FiO}_2$  0.5 and 1.0 decreased from 33 (31 to 35) to 13 (8 to 16) kPa ( $P = 0.008$ ) and from 71 (68 to 75) to 47 (21 to 52) kPa ( $P = 0.008$ ), respectively.  $C_{RS}$  decreased from 25 (23 to 27) to 9 (8 to 10) mL/cm  $\text{H}_2\text{O}$  ( $P = 0.008$ ) (Figure 6). Venous admixture with  $\text{FiO}_2$  1.0 (shunt fraction) increased from 7% (5 to 8%) to 19% (13 to 35%;  $P = 0.008$ ) with, as planned, a wide range (9 to 54%)

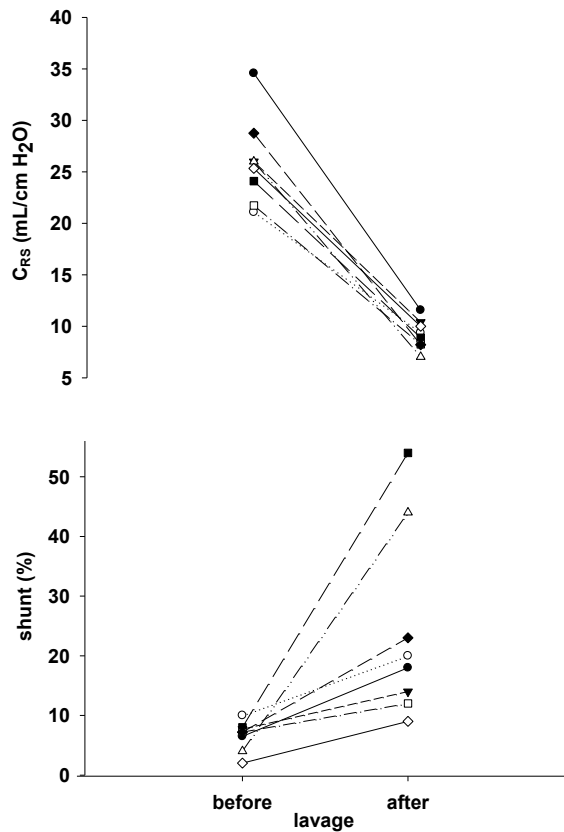


Figure 6. Effect of lung lavage on compliance ( $C_{RS}$ ) and shunt.

## Time to life-threatening hypoxemia

Without pharyngeal oxygen, the time to SpO<sub>2</sub> below 60% was 103 (88 to 111) sec, and with pharyngeal oxygen, three animals desaturated (after 55 sec, 85 sec, and 7 min), whereas the other five animals had adequate oxygenation during the whole 10-min study period ( $P = 0.016$ ). The individual PaO<sub>2</sub> values at the different time points are shown in Figure 7.

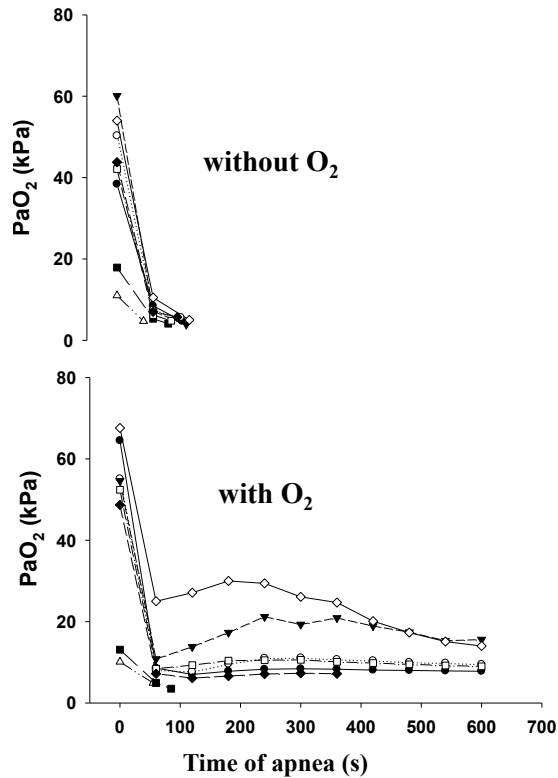


Figure 7. Partial pressure of oxygen in arterial blood (PaO<sub>2</sub>) versus time of apnea without (upper panel) and with (lower panel) pharyngeal oxygen administration. The symbols and lines depict the individual values.

## Relationship between shunt and time to life-threatening hypoxemia

There is a close correlation between shunt and time to desaturation (Figure 8). If 600 sec are used in the equation for the animals that did not desaturate during the study period, the equation is: time (sec) = 937 - 8.5 × shunt (%) ( $R^2 = 0.81$ ,  $P = 0.002$ ). When the shunt was less than 20%, no desaturation

occurred during the 10-min time frame, but when the shunt was above 44%, desaturation occurred within 90 sec.

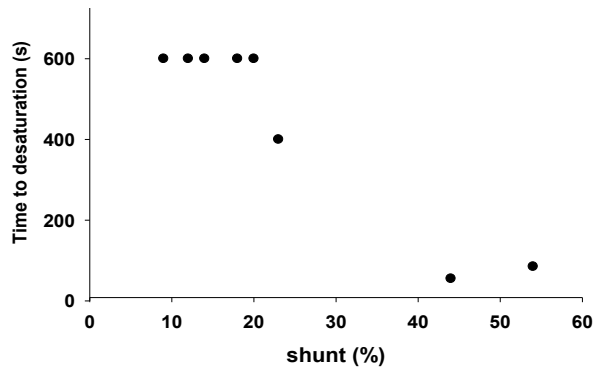


Figure 8. Time to desaturation below 60% as estimated by pulse oximetry versus shunt fraction on pharyngeal oxygen administration. The dots depict the individual values.

## Carbon dioxide and pH during apnea

During the 10-min apnea period with pharyngeal oxygen, PaCO<sub>2</sub> increased from 6.4 (6.2 to 7.0) to 17.1 (16.3 to 17.3) kPa ( $P < 0.05$ ) and pH decreased from 7.36 (7.34 to 7.38) to 7.03 (7.02 to 7.05;  $P < 0.05$ ).

## Hemodynamics

Lung lavage did not affect hemodynamics significantly, whereas prolonged apnea was associated with an increase in heart rate from 78 (65 to 92) to 102 (87 to 109) bpm ( $P = 0.023$ ), MAP from 80 (70 to 91) to 94 (84 to 93) mmHg ( $P = 0.03$ ), and mean pulmonary arterial pressure from 22 (18 to 25) to 33 (28 to 39) mmHg ( $P = 0.004$ ).

## Paper II

### Clinical study

Twelve women and 28 men (two with severe, 25 with moderate, and 13 with mild ARDS)<sup>72</sup> were enrolled (Table 1); eight were ventilated with pressure support ventilation, 12 with pressure-controlled ventilation, and 20 with PRVC; 39 of the subjects were orally intubated, and one had a tracheal cannula. PEEP was  $12.0 \pm 4.0$  cm H<sub>2</sub>O, FiO<sub>2</sub> was  $0.5 \pm 0.1$ , and the PaO<sub>2</sub>/FiO<sub>2</sub> ratio was 24



$\pm 6$  kPa. The mean time on the ventilator was  $8.6 \pm 9.9$  days. The tube sizes used in the studied subjects had an inner diameter of 7 mm in women ( $n = 12$ ) and an inner diameter of 8 mm in men ( $n = 28$ ). The gas was humidified with a heat-moisture exchanger in 20 subjects and with an active humidifier in the remaining subjects ( $n = 20$ ).

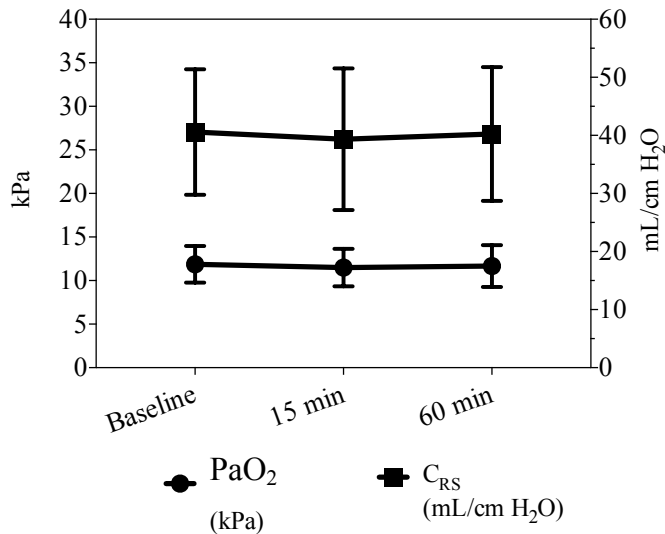


Figure 9. Mean partial pressure of oxygen in arterial blood (PaO<sub>2</sub>) and mean compliance of the respiratory system (C<sub>RS</sub>) with SD before the high-efficiency particulate air filter change and, 15 min and, 60 min after.

The mean duration of the filter exchange was  $3.5 \pm 1.2$  sec. There were no significant changes in PaO<sub>2</sub> ( $12 \pm 2$  kPa at baseline vs  $12 \pm 2$  kPa at 15 min and  $12 \pm 2$  kPa at 60 min,  $P < 0.24$ ; Table 2, Figure 9) or in C<sub>RS</sub> ( $41 \pm 11$  mL/cm H<sub>2</sub>O at baseline vs  $40 \pm 12$  mL/cm H<sub>2</sub>O at 15 min and  $40 \pm 12$  mL/cm H<sub>2</sub>O at 60 min,  $P < 0.32$ ; Table 2, Figure 9). Arterial pH ( $7.39 \pm 0.07$  at baseline vs  $7.39 \pm 0.08$  at 15 min and  $7.39 \pm 0.08$  at 60 min) and PaCO<sub>2</sub> ( $6 \pm 1$  kPa at baseline vs  $6 \pm 1$  kPa at 15 min and  $6 \pm 2$  kPa at 60 min) as well as hemodynamics (heart rate  $88 \pm 23$  bpm at baseline vs  $88 \pm 21$  bpm at 15 min and  $87 \pm 20$  bpm at 60 min [MAP  $77 \pm 14$  mmHg at baseline vs  $75 \pm 15$  mmHg at 15 min and  $75 \pm 10$  mmHg at 60 min]) did not change during the study period.

In the four subjects (No. 17, 35, 38, and 39, all ventilated with PRVC) in whom the pressure below the ETT was measured, the airway pressure was maintained above PEEP in all subjects during the 3 to 3.5 sec disconnection period (Table 3).

Age, yr	64 ± 15
Female sex, no. (%)	12 (30)
SAPS 3	67 ± 14
Duration of mechanical ventilation, d	8.6 ± 9.9
ICU stay, d	10 ± 11
Hospital stay, d	31 ± 38
ICU mortality, no. (%)	5 (13)
30 days mortality, no. (%)	9 (23)
ARDS	
Mild, no. (%)	13 (32.5)
Moderate, no. (%)	25 (62.5)
Severe, no. (%)	2 (5)
Mechanical ventilation settings	
Tidal volume, mL/kg	7.2 ± 1.6
Respiratory rate, breaths/min	12 ± 5
FiO <sub>2</sub>	0.5 ± 0.1
EIP, cm H <sub>2</sub> O	24 ± 5
PEEP, cm H <sub>2</sub> O	12 ± 4
Gas exchange	
Arterial pH	7.39 ± 0.07
PaCO <sub>2</sub> , kPa	6 ± 2
PaO <sub>2</sub> , kPa	12 ± 2
C <sub>RS</sub> , mL/cm H <sub>2</sub> O	41 ± 11
BE, mmol/L	1.0 ± 4.9
Circulatory parameters	
Mean arterial pressure, mmHg	77 ± 14
Puls rate, beats/min	88 ± 23

Values are mean ± SD unless otherwise specified.

ARDS acute respiratory distress syndrome, BE base excess, C<sub>RS</sub> compliance of the respiratory system, EIP end-inspiratory plateau pressure, FiO<sub>2</sub> fraction of inspired oxygen, PaCO<sub>2</sub> partial pressure of carbon dioxide in arterial blood, PaO<sub>2</sub> partial pressure of oxygen in arterial blood, PEEP positive end expiratory pressure, SAPS 3 Simplified Acute Physiology Score.

Table 2. *Subject Characteristics (n = 40)*

Subject#	ARDS	PaO <sub>2</sub> /FiO <sub>2</sub> (kPa)	PEEP (cm H <sub>2</sub> O)	PaO <sub>2</sub> (kPa)			C <sub>RS</sub> (mL/cm H <sub>2</sub> O)		
				Baseline	15 min	60 min	Baseline	15 min	60 min
1	2	21	17	13	13	11	53	53	60
2	3	31	15	15	16	13	40	37	37
3	3	27	12	16	11	11	*	*	*
4	3	30	11	16	14	13	37	34	37
5	1	11	13	9	8	8	48	44	44
6	2	26	16	14	16	19	40	30	35
7	2	17	17	10	8	8	38	30	28
8	2	16	17	10	9	9	22	27	26
9	2	14	13	10	10	10	43	42	43
10	2	22	17	12	11	11	43	45	45
11	2	19	17	9	9	9	25	25	22
12	1	12	12	9	9	10	53	50	55
13	2	15	16	11	11	11	33	29	30
14	2	19	12	11	11	11	35	35	42
15	2	21	16	12	12	12	40	30	35
16	3	31	19	15	15	15	47	43	43
17	2	17	14	13	13	13	59	58	59
18	2	22	11	12	13	15	60	60	60
19	2	21	10	10	12	13	26	27	26
20	2	21	5	11	9	9	15	16	17
21	3	28	5	12	11	12	50	50	49
22	2	26	8	13	12	12	*	*	*
23	3	28	10	10	9	9	*	*	*
24	3	29	10	13	14	14	*	*	*
25	2	25	5	12	11	12	*	*	*
26	2	25	12	10	10	10	*	*	*
27	2	19	13	12	11	12	37	34	35
28	2	20	12	9	9	9	*	*	*
29	2	18	8	11	11	10	41	41	41
30	3	34	18	15	16	14	26	26	28
31	2	25	15	14	14	16	30	20	30
32	3	31	12	9	10	11	*	*	*
33	3	32	8	14	14	14	52	52	*
34	2	25	11	10	10	11	44	64	54
35	2	22	15	12	13	14	40	38	40
36	2	18	9	12	12	10	46	45	38
37	3	31	6	12	11	11	*	*	*
38	3	29	9	10	10	9	52	53	54
39	3	39	5	14	11	13	50	49	49
40	2	26	7	12	13	13	45	46	47
Mean		24	12	12	12	12	41	40	40
± SD		6	4	2	2	2	11	12	12

ARDS severity is divided in three classes: (1) severe, (2) moderate, and (3) mild. \*NA missing value due to spontaneous breathing. ARDS acute respiratory distress syndrome, C<sub>RS</sub> compliance of the respiratory system, PaO<sub>2</sub> partial pressure of oxygen in arterial blood, PaO<sub>2</sub>/FiO<sub>2</sub> partial pressure of oxygen in arterial blood/fraction of inspired oxygen, PEEP positive end expiratory pressure.

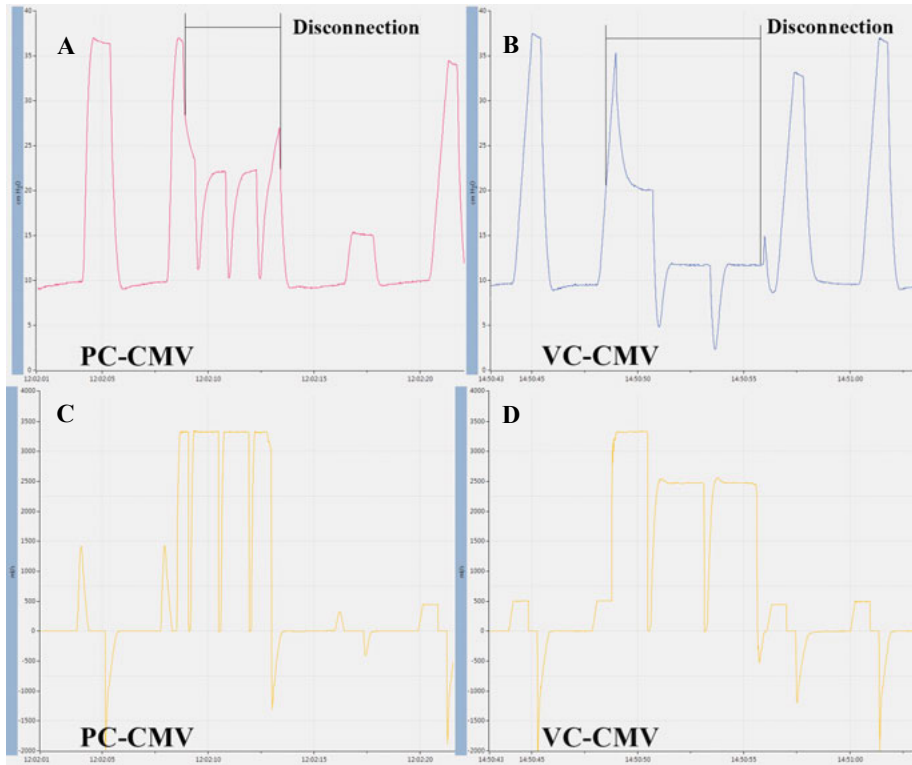
Subject#	Disconnection time (s)	ETT size (#)	PEEP (cm H <sub>2</sub> O)	P <sub>aw</sub> (cm H <sub>2</sub> O)
17	3.0	7	14	14
35	3.0	8	15	14
38	3.0	8	9	8
39	3.5	8	5	5

ETT endotracheal tube, P<sub>aw</sub> airway pressure, PEEP positive end expiratory pressure.

## Bench study

After disconnection of the ventilator circuit, the ventilator delivered four auto-triggered inspirations with a total duration of 3 to 10 sec, depending on the I:E ratio and the set breathing frequency. The inspiratory flow pattern differed between the two ventilation modes. In the pressure-controlled ventilation mode, the inspiratory flow reached a maximum rate of 3,300 mL/sec in 0.3 sec in all auto-triggered inspirations. In the volume-controlled ventilation mode, flow of the first triggered inspiration was the same as with the pressure-controlled ventilation (3,300 mL/sec) mode, but flow took 1.2 sec to reach its maximum rate. Flow in the volume-controlled ventilation mode decreased in inspiration numbers 2, 3, and 4 to 2,500 mL/sec. With pressure controlled-ventilation, P<sub>aw</sub> was maintained above the set PEEP of 10 cm H<sub>2</sub>O in all cases. The lowest P<sub>aw</sub> (12 ± 1.2 cm H<sub>2</sub>O) was independent of other settings and tube sizes.

However, with volume-controlled ventilation, P<sub>aw</sub> decreased to a minimum of 4.3 ± 1.2 cm H<sub>2</sub>O (P < 0.001 compared with pressure-controlled ventilation) (Figure 10). In both pressure-controlled ventilation and volume-controlled ventilation, P<sub>aw</sub> decreased to 0 cm H<sub>2</sub>O 0.7 ± 0.2 sec after the auto-triggered inspirations discontinued. With the suction support function activated, P<sub>aw</sub> decreased to 0 cm H<sub>2</sub>O within 1.7 ± 0.4 sec after disconnection (Figure 11), and the same pattern occurred with the -20 cm H<sub>2</sub>O trigger setting.



*Figure 10.* Airway pressure ( $P_{aw}$ ) 1 cm below an inner diameter 8 mm endotracheal tube tip during experimental high-efficiency particulate air filter change in the bench model. A and C: the ventilator was set at pressure controlled ventilation (PC-CMV) (end-inspiratory plateau pressure 25 cm H<sub>2</sub>O), breathing frequency of 15 breaths/min, ratio of inspiratory time to expiratory time 1:2, flow triggering 1 L/min. B and D: for volume controlled ventilation (VC-CMV), the settings were the same as during pressure controlled ventilation. The test lung was set to compliance 10 mL/cm H<sub>2</sub>O.

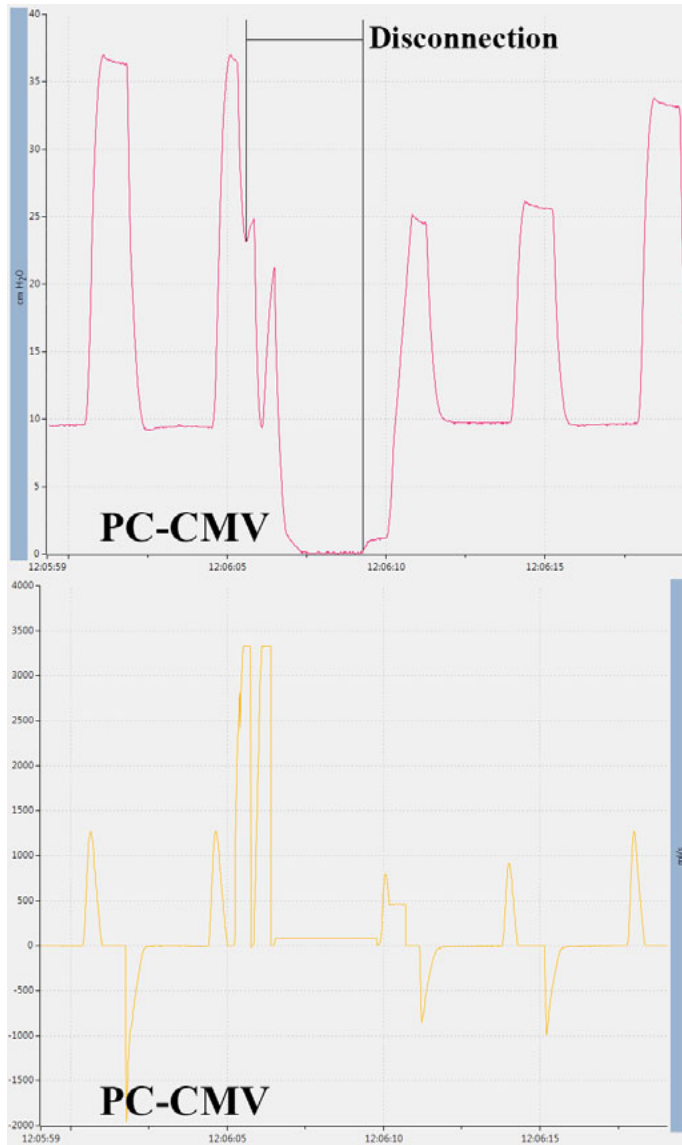


Figure 11. Airway pressure ( $P_{aw}$ ) 1 cm below inner diameter 8 mm endotracheal tube tip during experimental high-efficiency particulate air filter change in the bench model with suction support activated. The ventilator was set for pressure controlled ventilation (PC-CMV) (end-inspiratory plateau pressure 25 cm H<sub>2</sub>O), breathing frequency of 15 breaths/min, ratio of inspiratory time to expiratory time 1:2, flow triggering 1 L/min. The test lung was set to compliance 10 mL/cm H<sub>2</sub>O.

## Paper III

### Clinical study

Sixteen patients, three women and 13 men, admitted to the ICU were enrolled in this clinical observational study (Table 4).

All patients were orally intubated and mechanically ventilated using a Servo-i ventilator with an active humidifier (RT430). Five patients were ventilated with pressure control, seven with pressure-regulated volume control, three with pressure support, and one with neurally adjusted ventilatory assist (NAVA). PEEP was  $10 \pm 3$  cm H<sub>2</sub>O, FiO<sub>2</sub> was  $0.5 \pm 0.1$ , and the PaO<sub>2</sub>/FiO<sub>2</sub> ratio was  $23 \pm 5$  kPa. Five patients had moderate and 11 had mild ARDS. MAP was  $77 \pm 16$  mmHg, and the heart rate was  $88 \pm 18$  bpm. All 16 patients received hemodynamic support with noradrenaline (Abcur AB, Helsingborg, Sweden), and the mean dose was  $0.16 \pm 0.12$  mcg/kg/min. Two patients were treated with dobutamine (Dobutamin Hamel, Algo Pharma AB, Kista, Sweden), one with amiodarone (Cordarone<sup>®</sup>, Sanofi, Paris, France), two with levosimendan (Simdax<sup>®</sup>, Orion Pharma, Espoo, Finland) and one with vasopressin (Argipressin, Mercury Pharmaceuticals Ltd., London, UK) during the observational period. Six patients had continuous veno-venous renal replacement therapy, multiFiltrate<sup>®</sup> (Fresenius Kabi AB, Uppsala, Sweden) during the observational period.

The observational study was performed at  $3 \pm 4$  days (range 1 - 16) after admission to the ICU. The total mean duration of invasive ventilator support was  $10 \pm 11$  days, ICU stay  $12 \pm 13$  days, and hospital stay  $43 \pm 62$  days (Table 5). Three patients (19%) died during the ICU stay, four (25%) during hospital stay, and six patients (38%) died within the first 60 days after admission.

Table 4. Patient characteristics at the start of the study and outcome data (n = 16)

Variables	
Age, yr	68 ± 12
Female sex, no. (%)	3 (19)
SAPS 3	69 ± 15
SOFA	7 ± 4
Duration of mechanical ventilation, d	10 ± 11
ICU stay, d	12 ± 13
Hospital stay, d	43 ± 62
ICU mortality, no. (%)	3 (19)
Hospital mortality, no. (%)	4 (25)
60 days mortality, no. (%)	6 (38)
ARDS	
Mild, no. (%)	5 (31)
Moderate, no. (%)	11 (69)
Severe, no. (%)	0
Mechanical ventilation settings	
Tidal volume, mL/kg	7.3 ± 1.5
Respiratory rate, breaths/min	20 ± 5
FiO <sub>2</sub>	0.5 ± 0.1
Ppeak, cm H <sub>2</sub> O	21 ± 6
PEEP, cm H <sub>2</sub> O	10 ± 3
Gas exchange	
Arterial pH	7.40 ± 0.06
PaCO <sub>2</sub> kPa	6 ± 1
PaO <sub>2</sub> kPa	10 ± 1
BE, mmol/L	2.0 ± 4.5
Circulatory parameters	
Mean arterial pressure, mmHg	77 ± 16
Puls rate, beats/min	88 ± 18
Noradrenalin, mcg/kg/min	0.16 ± 0.12

Data are presented as mean ± SD.

ARDS acute respiratory distress syndrome, BE base excess, FiO<sub>2</sub> fraction of inspired oxygen, PaCO<sub>2</sub> partial pressure of carbon dioxide in arterial blood, PaO<sub>2</sub> partial pressure of oxygen in arterial blood, Ppeak end-inspiratory peak pressure, SAPS 3 Simplified Acute Physiology Score, SOFA Sequential Organ Failure Assessment Score.

Six hundred ninety-six procedures generated 699 AEs (mean 1.0 AE/procedure) and 158 SAEs (0.2 SAE/procedure) during 187 observational hr. One observation was aborted after 7 hr due to intrahospital transportation to another ICU. None of these adverse events were documented in the medical chart or reported to supervisors by the nursing staff.

The most common procedure was patient position change (24%), which also generated the majority of AEs (54%) and SAEs (61%). The second most common procedure (16%) was drug-administration-related, and the third most common procedure (13%) was blood sampling from arterial and central venous catheters (Table 6).

The procedure that generated the second most AEs (12%), was the category “Other”, which included oral care, subglottic suctioning, position change/manipulation of the endotracheal tube, shaving, eye care, and all procedures related to the feeding tube and measurement of cuff pressure of the endotracheal tube. The procedure generating the third most AEs (9%) was endotracheal suctioning.



**Table 5. Individual characteristics for all patients (n = 16)**

Patient#	Age (yr)	Gender (M/W)	FiO <sub>2</sub>	PEEP (cm H <sub>2</sub> O)	T <sub>V</sub> /PBW (mL/kg)	SAPS 3	SOFA	Duration of MV (d)	ICU-stay (d)	PaO <sub>2</sub> /FiO <sub>2</sub>	ARDS	MAP (mmHg)	Pulse (mcg/kg/min)	Noradrenalin (mcg/kg/min)
1	61	M	0.40	16	7.1	66	11	3	17	173	Moderate	64	72	0.20
2	85	M	0.50	10	6.6	73	9	2	7	158	Moderate	93	73	0.06
3	83	M	0.60	10	7.9	85	9	2	11	135	Moderate	89	79	0.20
4	64	M	0.45	10	8.3	55	9	2	5	210	Mild	100	75	0.10
5	64	M	0.60	14	4.6	62	9	4	18	128	Moderate	76	116	0.10
6	74	M	0.35	8	7.5	86	6	11	7	233	Mild	98	75	0.11
7	42	M	0.40	10	6.1	77	7	1	5	240	Mild	73	118	0.05
8	53	M	0.40	10	6.8	63	6	6	46	165	Moderate	70	82	0.08
9	79	W	0.60	10	7.3	91	11	4	4	105	Moderate	52	104	0.56
10	64	M	0.40	8	8.0	69	7	5	7	203	Mild	65	83	0.11
11	69	M	0.30	8	7.2	51	5	2	7	210	Mild	93	110	0.08
12	70	M	0.40	8	7.1	64	14	4	6	188	Moderate	78	70	0.16
13	50	M	0.40	8	10.4	37	15	33	38	195	Moderate	54	107	0.26
14	76	W	0.60	12	5.1	89	10	6	7	120	Moderate	94	80	0.21
15	75	W	0.45	14	9.6	72	9	2	2	165	Moderate	65	69	0.10
16	82	M	0.45	8	6.6	58	10	3	3	143	Moderate	65	101	0.12
<b>Mean</b>	<b>68</b>		<b>0.5</b>	<b>10</b>	<b>7.3</b>	<b>69</b>	<b>9</b>	<b>6</b>	<b>12</b>	<b>173</b>		<b>77</b>	<b>88</b>	<b>0.16</b>
<b>SD</b>	<b>12</b>		<b>0.1</b>	<b>2</b>	<b>1.4</b>	<b>14</b>	<b>3</b>	<b>7</b>	<b>12</b>	<b>39</b>		<b>15</b>	<b>17</b>	<b>0.12</b>

ARDS acute respiratory distress syndrome, *Duration of MV* duration of mechanical ventilation, *FiO<sub>2</sub>* fraction of inspired oxygen, *MAP* mean arterial pressure, *PaO<sub>2</sub>/FiO<sub>2</sub>* partial pressure of oxygen in arterial blood/fraction of inspired oxygen, *PEEP* positive end expiratory pressure, *SAPS 3* Simplified Acute Physiology Score, *SOFA* Sequential Organ Failure Assessment Score, *T<sub>V</sub>/PBW* tidal volume divided by predicted body weight.

**Table 6. Procedures divided by patient**

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Total	(%)
Patient position change	13	7	19	15	12	14	12	17	5	13	6	5	5	8	7	6	164	24%
Drug related	9	3	5	10	10	9	9	9	11	9	9	1	5	3	5	4	111	16%
Blod sampling	4	7	5	6	6	5	5	7	10	5	3	6	5	4	7	4	89	13%
Other	2	5	2	2	6	7	3	5	5	9	3	5	4	8	3	7	76	11%
Ventilator disconnection	1	1	8	16	4	9	4	1	1	6	2	5	11	0	5	1	75	11%
Endotracheal suctioning	3	3	4	15	3	2	0	0	0	3	2	6	13	0	5	0	59	8%
Clinical examination	2	5	3	4	3	4	4	2	4	3	4	3	3	3	3	4	54	8%
Wound care	5	0	0	3	0	0	1	2	1	0	1	1	0	1	1	1	17	2%
Chest x-ray, ultrasound	0	0	2	0	3	2	0	1	3	1	0	0	1	1	1	1	16	2%
Physical therapy	2	0	1	1	1	2	2	1	2	1	0	0	1	0	1	0	15	2%
Medical procedures	0	2	3	0	4	1	1	0	0	2	0	0	0	0	0	0	13	2%
Insertion of IV catheters	0	0	0	0	0	3	0	0	1	0	0	0	0	0	0	0	4	0.6%
Intra-hospital transportation	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	3	0.4%
<b>Total</b>	<b>41</b>	<b>34</b>	<b>52</b>	<b>72</b>	<b>52</b>	<b>59</b>	<b>41</b>	<b>45</b>	<b>43</b>	<b>52</b>	<b>31</b>	<b>32</b>	<b>48</b>	<b>28</b>	<b>38</b>	<b>28</b>	<b>696</b>	
	6%	5%	7%	10%	7%	8%	6%	6%	6%	7%	4%	5%	7%	4%	5%	4%		

The most common AEs (35%) were changes in MAP (both increase and decrease), coughing (15%), and elevation in respiratory rate (11%) (Table 7).

The most common SAEs were oxygen desaturation (29%), ventilatory distress (28%), and hypotension (22%). The procedure generating the second most common SAE (12%) was drug administration related. The procedure generating the third most common SAE (8%), was clinical examination and the category “Other” (Table 8).

Table 7. Adverse events divided by the eight most AE generating procedures

	Patient position change		Endotracheal suctioning	Clinical examination	Drugrelated	Medical procedures	Physical therapy	Insertions of IV-lines	Total	(%)
	Other									
Bloodpressure ↑ (MAP), no.	69	22	21	12	7	11	9	0	151	22%
Cough, no.	63	11	14	6	0	6	3	0	103	15%
Bloodpressure ↓ (MAP), no.	48	4	2	3	21	9	2	1	90	13%
Respiratory rate ↑ (/min), no.	47	8	6	7	1	1	6	0	76	11%
Oxygen Desaturation, no.	40	7	4	5	7	2	0	0	65	9%
Wakening (RASS ↑), no.	23	14	12	4	1	1	1	0	56	8%
Ventilatory distress, no.	26	4	2	2	0	1	1	0	36	5%
Loss of SpO <sub>2</sub> -monitoring, no.	31	2	1	1	0	0	0	0	35	5%
Uneasiness, no.	7	7	3	1	1	1	0	0	20	3%
Pulse ↑ (/min), no.	9	2	1	2	1	1	0	0	16	2%
Ventilator disconnection*, no.	9	0	0	1	0	0	0	0	10	1%
Respiratory rate ↓ (/min), no.	1	1	0	1	4	0	0	0	7	1%
Loss of ECG-monitoring, no.	2	0	0	0	0	0	0	0	2	0,3%
Pulse ↓ (/min), no.	1	0	0	0	0	0	0	0	1	0,1%
Total	376	82	66	45	43	33	22	1	699	†
	54%	12%	9%	6%	6%	5%	3%	0,1%		

†Total amount of AE in all procedures. Procedures not included in the table: Blood sampling, Ventilation disconnection, Wound care, Chest x-ray and ultrasound. ECG electrocardiography, IV-lines intravenous lines, MAP mean arterial pressure, SpO<sub>2</sub> peripheral capillary oxygen saturation by oximetry, RASS Richmond Agitation-sedation Scale.

Table 8. Serious adverse events (SAE) divided by procedure

	Patient position change		Clinical examination	Other	Endotracheal suctioning	Physical therapy	Medical procedures	Insertions of IV-lines	Total	(%)
	Drugrelated									
Oxygen Desaturation, n.	28	4	3	4	3	1	2	0	45	29%
Ventilatory distress, n.	34	0	2	4	2	2	0	0	44	28%
Hypotension, n.	20	9	2	1	1	0	1	1	35	22%
Hypertension, n.	8	2	1	2	3	2	0	0	18	11%
Tachycardia, n.	1	0	2	1	0	0	0	0	4	3%
Bradycardia, n.	2	2	0	0	0	0	0	0	4	3%
Bradypnea, n.	1	2	1	0	0	0	0	0	4	3%
Arrhythmias, n.	3	0	1	0	0	0	0	0	4	3%
Total	97	19	12	12	9	5	3	1	158	
	61%	12%	8%	8%	6%	3%	2%	1%		

Definition of SAE:

Tachycardia: heart rate  $\geq 110$  bpm if  $< 100$  bpm before the procedure; bradycardia: heart rate  $\leq 60$  bpm if  $> 70$  bpm before; hypertension: MAP  $\geq 110$  mmHg if  $< 100$  mmHg before; hypotension: MAP  $\leq 60$  mmHg if  $> 70$  mmHg before; desaturation: SpO<sub>2</sub>  $\leq 90\%$  if  $> 92\%$  before; bradypnea: respiratory rate  $\leq 10$  /min if  $> 10$  /min before; ventilatory distress: severe ventilator asynchrony (nonstop coughing, not possible to mechanically ventilate and/or tachypnea (respiratory rate  $\geq 35$  /min if it was  $< 35$  /min); cardiac arrest and serious arrhythmia. IV-lines intravenous lines.

## Survey of risk awareness of nursing procedures

The survey were sent to 62 CCRNs, and 45 (73%) responded within the stipulated time frame of 2 weeks. All CCRNs reported that they performed patient position change to avoid pressure ulcers and to recruit atelectatic lung regions. A majority (75%) reported that they changed the patient's position in order to improve hemodynamics and blood oxygen saturation. However, 58% also reported that they considered that the highest risk related to position change was ventilatory compromise (desaturation, ventilator-patient asynchrony and/or tachypnea), and 97% reported that they sometimes abstained from turning a patient for of this reason. All CCRNs reported that they considered that a body position change could sometimes or commonly be painful for the patient. Eighty-six percent of the CCRNs often gave a bolus of analgesics  $5 \pm 4$  min before changing a patient's body position. Eighty-nine percent of the CCRNs regarded endotracheal suctioning as a painful procedure.

Despite this, only 5% reported that they gave analgesics before endotracheal suctioning. Ninety-seven percent reported that they seldom pre-oxygenated the patient before position change. On the other hand, all CCRNs stated that they pre-oxygenated the patients routinely before endotracheal suctioning.

## Paper IV

One hundred and twelve patients, 29 women and 83 men, were enrolled in this study. General characteristics are presented in Table 9.

The mechanism of injury is presented in Figure 12. Motor-vehicle accidents were the most common cause followed by falls. In 16 patients (15 falls and one motor vehicle accident), the trauma was related to a suicide attempt.

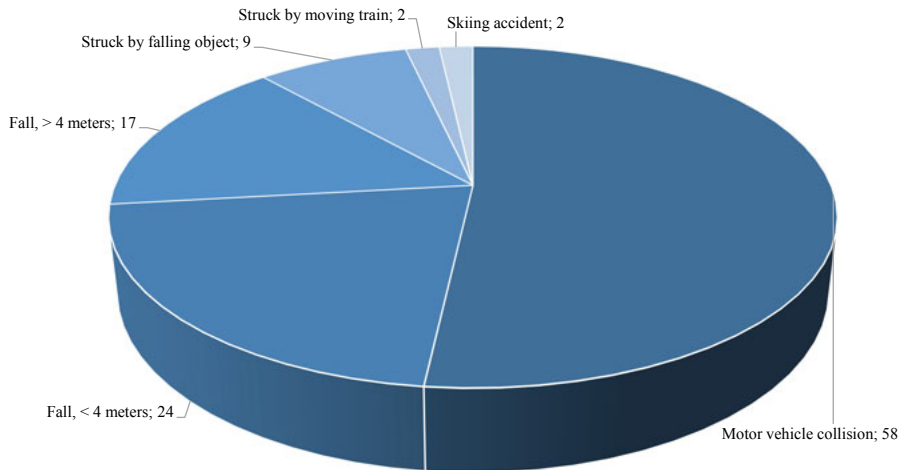


Figure 12. Mechanism of injury. The numbers depict number of patients per category (n = 112).

## AHF/ARDS

The total incidence of AHF/ARDS was 67% (75/112 patients), i.e., the percentage of patients that at any period during the ICU stay fulfilled the AHF/ARDS criteria, and the allocation to the two groups was done according to the analyses of the chest images.

### Analysis of the chest images

One hundred and forty-eight chest images were analyzed (87 images pre- (78% of the patients) and 61 post-operative (54% of the patients)). There was a lack of consensus in 17 images, eight pre- (9% of the analyzed images) and

Table 9. Characteristics for all patients and all patients with and without acute hypoxic failure or acute respiratory distress syndrome

Variable	All patients (n = 112)	Patients with AHF (n = 49 (44%))	Patients with ARDS (n = 26 (23%))	Patients with no AHF/ARDS (n = 37 (33%))	P value
Age (yrs)	48 ± 18	48 ± 19	51 ± 19	46 ± 18	0.56
Female sex, no. (%)	29 (26)	13 (27)	5 (19)	11 (30)	0.65
Injury severity score (ISS)	29 ± 12	30 ± 13	29 ± 11	26 ± 11	0.27
New Injury severity score (NISS)	32 ± 12	33 ± 13	30 ± 11	30 ± 12	0.31
Simplified Acute Physiology Score (SAPS 3)	45 ± 10	45 ± 10	45 ± 10	45 ± 10	0.80
Sequential Organ Failure Assessment score (SOFA)	7 ± 4	<b>9 ± 4<sup>a</sup></b>	<b>7 ± 3<sup>a</sup></b>	5 ± 3	<b>&lt; 0.0001</b>
Glasgow Coma Scale (GCS)	13 ± 3	<b>11 ± 4<sup>a,b</sup></b>	14 ± 2	14 ± 3	<b>&lt; 0.001</b>
Diabetes, no. (%)	14 (13)	7 (14)	5 (19)	2 (5)	0.24
Blunt injury mechanism, no. (%)	112 (100%)	49 (100)	26 (100)	37 (100)	n.a.
Pelvis fracture type					
Acetabular, no. (%)	39 (35)	15 (31)	11 (42)	13 (35)	0.61
Ring injury, no. (%)	63 (57)	29 (59)	13 (50)	22 (60)	0.71
Combined, no. (%)	9 (8)	5 (10)	2 (8)	2 (5)	0.72
Flail chest, no. (%)	2 (2)	2 (4)	0 (0)	0 (0)	0.28
Pulmonary contusion, no. (%)	27 (24)	12 (25)	<b>11 (42)<sup>a</sup></b>	4 (11)	<b>0.02</b>
Pneumothorax before admission, no. (%)	43 (38)	20 (41)	12 (46)	11 (30)	0.38
Pulmonary embolism, no. (%)	7 (6)	4 (8)	2 (8)	1 (3)	0.56
Pneumonia, no. (%)	16 (14)	8 (16)	<b>7 (27)<sup>a</sup></b>	1 (3)	<b>0.02</b>
Time to surgery after injury, d	6 ± 4	7 ± 4	6 ± 3	5 ± 4	0.25
Perioperative blood loss, mL	1085 ± 1419	834 ± 831	1573 ± 2330	1034 ± 1025	0.44
Need of invasive respiratory support, no. (%)	55 (49)	<b>29 (59)<sup>a</sup></b>	<b>15 (58)<sup>a</sup></b>	11 (30)	<b>&lt; 0.0001</b>
Need of non-invasive respiratory support, no. (%)	4 (4)	1 (2)	1 (4)	2 (5)	0.61
Duration of mechanical ventilation, d	4 ± 4	<b>5 ± 4<sup>a</sup></b>	<b>4 ± 2<sup>a</sup></b>	2 ± 2	<b>&lt; 0.001</b>
Need of vasoactive drugs, no. (%)	40 (36)	<b>23 (47)<sup>a</sup></b>	11 (42)	6 (16)	<b>0.009</b>
Duration with vasoactive drugs, d	3 ± 3	<b>3 ± 4<sup>a</sup></b>	<b>3 ± 2<sup>a</sup></b>	1 ± 1	<b>0.02</b>
Renal failure during ICU stay, no. (%)	19 (17)	10 (20)	6 (23)	3 (8)	0.21
ICU stay, d	6 ± 9	7 ± 7	6 ± 5	5 ± 13 <sup>#</sup>	0.76
Hospital stay, d	39 ± 23	42 ± 26	36 ± 19	37 ± 22	0.66
ICU mortality, no. (%)	4 (4)	3 (6)	1 (4)	0 (0)	0.32
Hospital mortality, no. (%)	5 (5)	4 (8)	1 (4)	0 (0)	0.19
60 days mortality, no. (%)	5 (5) <sup>##</sup>	4 (8) <sup>##</sup>	1 (4)	0 (0)	0.19
Crystalloids, L/24 hrs	3596 ± 1261	3434 ± 964	3318 ± 1348	3888 ± 1460	0.08
Colloids*, L/24 hrs	541 ± 608	442 ± 495	613 ± 569	623 ± 754	0.12
Hemoglobin pre-operative, g/L	102 ± 14	102 ± 14	99 ± 14	105 ± 15	0.28
Hemoglobin post-operative, g/L	100 ± 12	101 ± 12	97 ± 10	99 ± 13	0.32
Rbc transfusion rate, units/24 hrs	2 ± 4	<b>2 ± 1<sup>a</sup></b>	2 ± 2	4 ± 7	<b>0.03</b>
Fresh frozen plasma transfusion rate, units/24 hrs	1 ± 3	1 ± 1	1 ± 2	2 ± 5	0.11

Data are mean ± SD unless otherwise specified. The overall significance level is shown (ANOVA) <sup>a</sup>*P* < 0.05 compared with patients with no AHF/ARDS. <sup>b</sup>*P* < 0.05 compared with patients with ARDS (Tukey test). \*Synthetic colloids and albumin, <sup>#</sup>One patient treated in the Neuro-intensive care unit for 81 days, <sup>##</sup>One patient was in palliative care before the trauma. *AHF* acute hypoxic failure, *ARDS* acute respiratory distress syndrome, *ICU* intensive care unit, *rbc* red blood cell concentrate.

nine (15% of the analyzed images) post-operative. After a second analysis consensus was found in the remaining 17 images. Chest images were divided by 102 chest radiograms and 46 CT scans. The radiological examinations were performed  $2 \pm 3$  days before surgery and  $2 \pm 3$  days after surgery. In 12 patients with AHF before surgery and 20 patients with AHF after surgery, no chest were images available.

### Incidence of AHF

The total incidence of AHF was 44% (49/112 patients). Thirty-five patients (31%) had AHF before surgery (14 patients with mild AHF, 18 patients with moderate AHF and three patients with severe AHF); 39 patients (35%) had AHF after surgery (13 patients with mild AHF, 21 patients with moderate AHF and five patients with severe AHF); and 25 patients (22%) had AHF both before and after the surgical intervention.

### Incidence of ARDS

The total incidence of ARDS was 23% (26/112 patients). Twelve patients (11%) had ARDS before surgery (four patients with mild ARDS, seven patients with moderate ARDS and one patient with severe ARDS); 20 patients (18%) had ARDS after surgery (four patients with mild ARDS, 15 patients with moderate ARDS and one patient with severe ARDS) and six patients (5%) had ARDS both before and after surgery.

There was no major change in the yearly incidence of AHF/ARDS in patients with ICU requiring pelvis fractures from 2007 to 2014 (Figure 13).

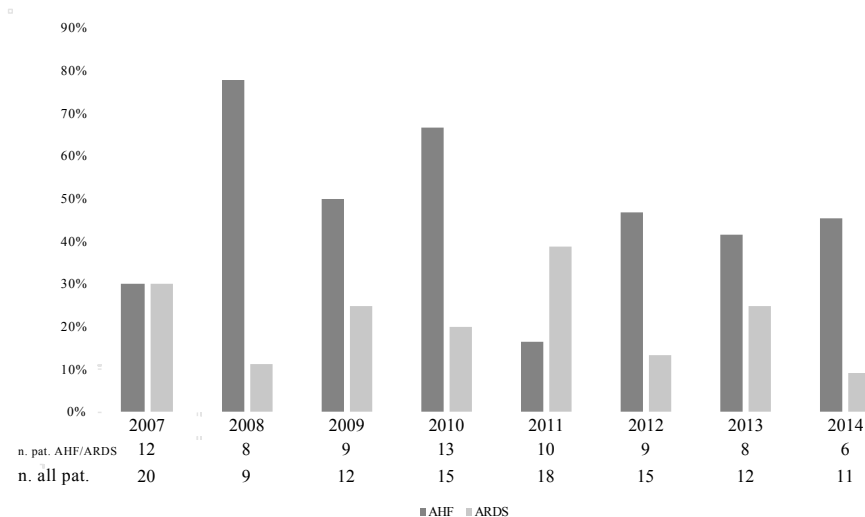


Figure 13. Incidence of acute hypoxic failure (AHF) and acute respiratory distress syndrome (ARDS) per year 2007 to 2014. n. pat. AHF/ARDS number of patients with AHF/ARDS, n. all pat. total number of patients.

### **Characteristics of patients with and without AHF/ARDS**

In Table 9, the patients are presented in three groups: two groups in which the patients had AHF or ARDS during the ICU stay and one group which never developed AHF or ARDS. There were no differences in severity scores (ISS, NISS) between patients with or without AHF/ARDS. As expected, the Sequential Organ Assessment Scores (SOFA) were higher in patients with AHF/ARDS than in the other patients, since the PaO<sub>2</sub>/FiO<sub>2</sub> ratio is included in the calculation of SOFA. The patients with AHF/ARDS had more lung contusions and had been diagnosed more frequently with pneumonia than the other patients had. This resulted in more need of invasive mechanical ventilation as well as longer duration of mechanical ventilation. The patients with AHF/ARDS were more often treated with vasoactive agents, but there were no differences in the amount of fluid administered or blood product transfusions among the groups.

### **Effect of the surgical stabilization procedure (See Table 10)**

Twenty-three patients with pre-operative normal lung status developed AHF/ARDS in relation to the surgical procedure, whereas 12 patients with AHF/ARDS normalized their lung condition (Figure 14). The injury scores and the amount of fluid administered and blood product transfused were similar in the two categories. However, the patients who developed AHF/ARDS had a higher incidence of lung contusion ( $P = 0.04$ ). In addition, surgical stabilization was performed earlier (5 versus 10 days) in these patients ( $P = 0.03$ ). The individual changes of the patients AHF/ARDS status pre- versus post-operatively are displayed in Figure 14.

### **Mortality**

The ICU and hospital mortality was low. In the AHF group 8% died (4/49 patients), in the ARDS group 4% (1/26 patient), while in the group without AHF/ARDS none (0/37) died during the hospital stay. The deaths were not related to respiratory failure; one of the patients that died in the ICU was admitted post-operatively after a cardiac arrest in the orthopedics ward (year 2010), one patient died due to sepsis (year 2007), one patient due to cerebral herniation (year 2007), and one patient died due to multiorgan failure (year 2011). One patient that died within the first 60 days of admission was treated with palliative care before the trauma. No patient has died since 2011.

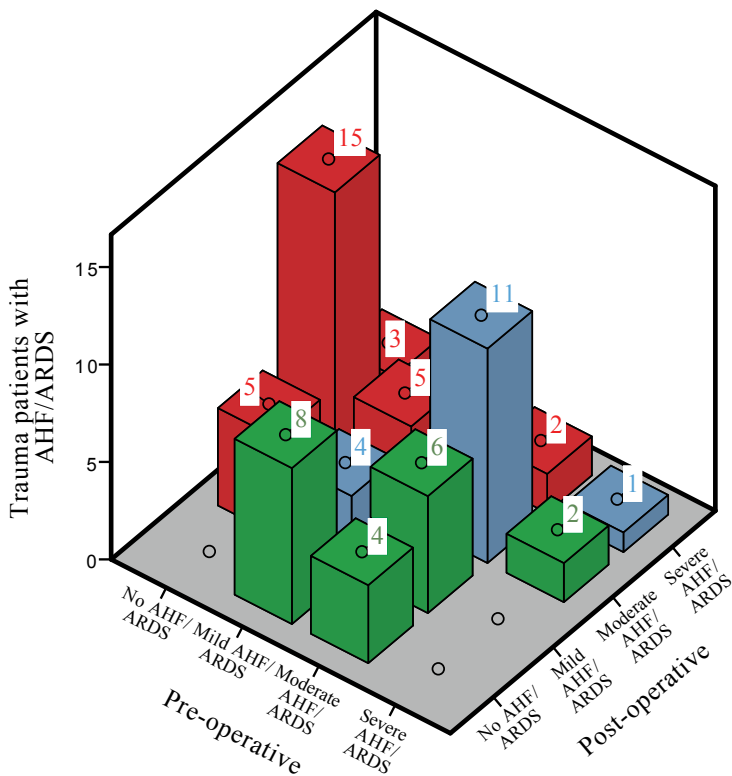


Figure 14. Patient with acute hypoxic failure (AHF) and acute respiratory distress syndrome (ARDS) and the individual status change pre- and post-operative. The color describes how the individual patient's AHF/ARDS status changed post-operatively. Red = Worsen AHF/ARDS status (e.g. 15 patients had no AHF/ARDS pre-operative but had moderate AHF/ARDS post-operative (the red number 15)). Blue = No AHF/ARDS status change (e.g. 11 patients had moderate AHF/ARDS pre-operative and post-operative (the blue number 11)). Green = Better AHF/ARDS status (e.g. two patients had severe AHF/ARDS pre-operative but had moderate AHF/ARDS post-operative (the green number 2)).

Table 10. *Effects of the surgical stabilization*

Variable	Negative AHF/ARDS status change (n =23)	Positive AHF/ARDS status change (n =12)	<i>P</i> value
Injury severity score (ISS)	26 ± 11	32 ± 9	0.08
Pulmonary contusion, no. (%)	<b>9 (39)</b>	<b>1 (8)</b>	<b>0.04</b>
Pneumothorax before admission, no. (%)	10 (44)	3 (25)	0.38
Pneumonia, no. (%)	2 (9)	3 (25)	0.70
Time to surgery after injury, d	<b>5 ± 3</b>	<b>10 ± 6</b>	<b>0.03</b>
PEEP pre-operative, cm H <sub>2</sub> O	9 ± 6	7 ± 2	0.30
PEEP post-operative, cm H <sub>2</sub> O	8 ± 4	8 ± 1	0.99
Perioperative blood loss, mL	1058 ± 1277	1261 ± 1095	0.68
Perioperative fluid balance, mL	2573 ± 1859	2205 ± 1669	0.70
Perioperative crystalloids, mL	3140 ± 978	3755 ± 1311	0.16
Perioperative colloids*, mL	818 ± 737	528 ± 643	0.31
Perioperative rbc transfusion rate, units	3 ± 3	2 ± 1	0.51
Fresh frozen plasma transfusion rate, units	2 ± 2	2 ± 2	0.72

Data are mean ± SD unless otherwise specified. \*Synthetic colloids and albumin. *PEEP* positive end expiratory pressure. *rbc* red blood cell concentrate.



# Discussion

The studies presented in this thesis have focused on patient safety issues of many different origins. Some will probably call this thesis divergent. However, our main goal have all the time been to increase the safety among critically ill patients from different angles but especially in the respiratory field. Therefore we believe that this thesis have an important theme and even though it seems divergent the common thread should be possible to see when reading the discussion.

## Increased safety with pharyngeal oxygen administration -at least for some

In the first study,<sup>73</sup> we used an experimental approach with a simple technique of pharyngeal oxygen administration. This technique is performed using a pharyngeal catheter inserted through one of the nostrils during pre-oxygenation, the main objective being to increase time to life-threatening hypoxemia ( $SpO_2 < 60\%$ ). Apneic oxygenation with pharyngeal oxygen administration as used in this study is far from new. It was first described by Draper and Whitehead in 1944, who performed experiments in anesthetized dogs.<sup>74</sup> In 1951, Enghoff & Holmdahl and colleagues evaluated the technique of apneic oxygenation in healthy volunteers and were able to show that adequate oxygenation could be achieved for a prolonged time.<sup>75</sup> Apneic oxygenation was then used in several different studies during the 1950s and was effective in preventing hypoxemia for up to 30 min in both animals and human subjects.<sup>76,77</sup> Apneic oxygenation was then unfortunately almost forgotten and is seldom used nowadays, except in the diagnosis of brain death. It was not until 1988 that Teller and colleagues<sup>78</sup> used the technique in anesthetized patients with healthy lungs and showed that the method could maintain adequate oxygenation for at least 10 min. They again showed that apneic oxygenation could be beneficial in situations where a prolonged time is needed to gain control of the airway.<sup>78</sup> Even so, the method is not included as a recommendation in the American Society of Anesthesiologist's (ASA) difficult airway algorithm.<sup>79</sup> To our knowledge, there were no studies preceding ours on the use of this technique in critically ill patients or in respiratory failure. We therefore evaluated this technique that is almost non-invasive, is associated with few adverse events, and has a considerable clinical potential in critically ill patients. Due to ethical considerations, the technique was not ready to be evaluated in critically

ill humans. We therefore used a porcine model to perform our experiments. We were able to show that pharyngeal oxygen administration increases time to life-threatening hypoxemia when the pulmonary shunt is below 25%.

In healthy, resting adults, oxygen is absorbed at a rate of approximately 250 mL per min. This creates a force that redistributes oxygen, if administered in the pharynx, into the lungs. Alveolar oxygen concentration therefore remains high for a prolonged time frame.<sup>76</sup> As observed in our study, carbon dioxide increased almost 2.7 times (6.4 -> 17.1 kPa), which led to a decreased pH of 0.33 (7.36 -> 7.03) during the 10-min apneic study time. However, in our opinion the fall in pH seems to be a less serious issue compared to other complications that could occur in a “cannot intubate, cannot ventilate” (CICV) scenario. According to the ASA difficult airway algorithm,<sup>79</sup> the only alternative left in the CICV situation is to perform an emergency cricothyrotomy to provide emergency oxygenation. The highest incidence of major airway complications is in the intensive care units, emergency departments,<sup>80</sup> and in pre-hospital settings.<sup>81</sup> Hypoxemia is the most common cause of airway-related deaths.<sup>82</sup>

Even though our study gave some answers to this huge scientific puzzle, many are left unanswered regarding apneic oxygenation and improvements of safety in tracheal intubation. As noted previously, our technique of pharyngeal oxygen administration at 10L/min had less effect if piglets had a high pulmonary shunt. Would it be possible to use another method to increase the oxygenation effect even in animals with high pulmonary shunt? We hypothesized that nasal high flow oxygen (NHFO) could be such a method. One of the suggested effects, besides providing a high inspired oxygen concentration, is that NHFO produces a continuous positive airway pressure (CPAP) that may prevent lung collapse and thus improve oxygenation.<sup>83,84</sup> The effect of CPAP is more pronounced when the mouth is closed, but even with the mouth open, Groves and colleagues<sup>85</sup> found a positive pressure in the pharynx of about 3 cm H<sub>2</sub>O when a flow of 65 L/min was used. We therefore decided to test this method in a similar fashion as in our previous study, but instead of a flow of 10 L/min, we used 65 L/min of oxygen.<sup>86</sup> However, this study in animals with tendency toward pronounced lung collapse (pulmonary shunt range 24 - 45% with zero end-expiratory pressure) showed that NHFO gave inconsistent CPAP levels, did not conclusively extend the time of safe oxygenation during apnea (Figure 15) and induced significant gastric dilation during laryngoscopy. This suggests that NHFO should be used cautiously in conjunction with tracheal intubation in acute hypoxic failure (AHF). Unfortunately, no journal has yet considered our NHFO study, mentioned above, to be suitable and therefore it is still unpublished.

However, many published studies have investigated apneic ventilation with low or high oxygenation flow.<sup>87-91</sup> Four of these studies<sup>88-91</sup> found that apneic oxygenation was associated with a reduction in the incidence of hypoxemia during intubation, which is consistent with our first study. These patients

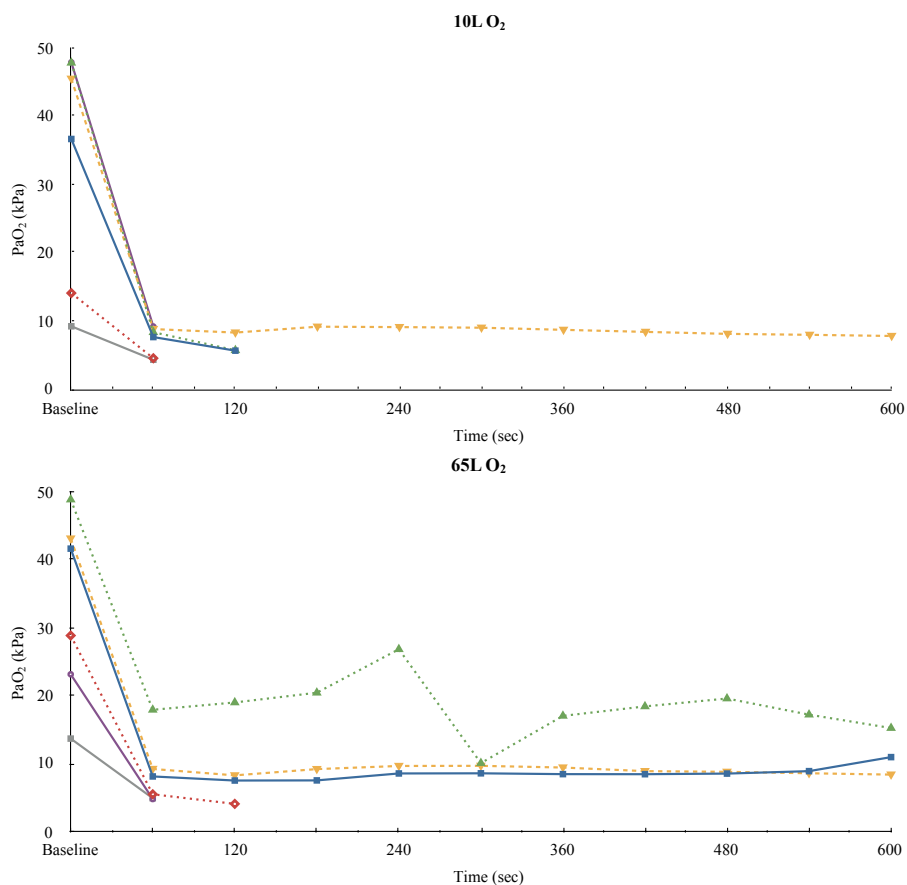


Figure 15. Partial pressure of oxygen in arterial blood (PaO<sub>2</sub>) versus time of apnea with nasal low flow oxygenation (10 L/min O<sub>2</sub>) and nasal high flow oxygenation (65 L/min O<sub>2</sub>). The symbols and lines depict the individual values.

were primarily intubated for traumatic, hemodynamic, or neurological conditions. Even though none of these studies have measured pulmonary shunt, it seems unlikely that the shunt fraction was high because the initial SpO<sub>2</sub> in many patients was above 95% before the intubation procedure. However, in the study by Semler and colleagues,<sup>87</sup> the indication for intubation was respiratory failure in 57% of the patients. They found that apneic oxygenation did not increase the lowest arterial oxygenation saturation during endotracheal intubation. This finding is consistent with our unpublished work and suggests that apneic oxygenation has a limited effect in patients with severe respiratory distress with high shunt fractions.

## Ventilator disconnection is always bad, is it not?!

In our second study,<sup>92</sup> we used a clinical approach in which we evaluated a daily routine ventilator-filter exchange. This procedure interrupts the integrity of the ventilator circuit that we thought led to a risk of a rapid development of atelectasis. The ventilator-filter exchange procedure was performed in all mechanically ventilated ICU patients at 5 AM every morning. We hypothesized that this procedure could seriously impair pulmonary function as assessed by arterial oxygenation and respiratory compliance, especially in critically ill patients. Contrary to our hypothesis, the results showed no deterioration in pulmonary function after the ventilator-filter exchange. In order to find an explanation for our results, we performed a bench study with a set-up that mimicked the clinical scenario. This study demonstrated that disconnection of the expiratory limb of the ventilatory circuit induces an auto-triggering behavior of the ventilator during the filter exchange procedure. This high-flow auto-triggering is the most likely mechanism behind the maintained airway pressure above the set PEEP in pressure-controlled ventilation modes, thus providing an explanation for the absence of deterioration in lung function that we found in patients during the study. With VC-CMV, which delivers a specific volume with a limited square wave flow pattern, the flow should not be high enough to maintain an adequate airway pressure level. However, unexpectedly, in the bench test the flow rate with VC-CMV increased to about 3,300 mL/sec after a short delay, corresponding to the set rise time and a flow trigger delay of 100 ms, inducing only a short drop in airway pressure (Figure 10). This is because the Servo-*i* has a “temporary pressure support” in the VC-CMV mode that is switched on when the inspiratory pressure drops 3 cm H<sub>2</sub>O in relation to the expected pressure value during inspiration, indicating that the flow demand of the patient is higher than the ventilator delivers, in combination with the lack of the feedback from expiratory flow meter. However, this temporary pressure support feature is model-dependent and can be deactivated in newer models of the Servo-*i* for the US market (Åke Larsson, Maquet Critical Care, personal communication).

In the power analysis, we a priori estimated the number of subjects using a high power (0.95). In fact, a power analysis a posteriori showed 0.99, indicating that it is not likely that filter exchange in the patient category studied leads to a deterioration in lung function. However, the clinical part was performed in patients without extremely high PEEP levels or FiO<sub>2</sub>. With very high PEEP, even during pressure control, the flow and resistance in the ventilator tubing might not be adequate to maintain a sufficient airway pressure. In patients needing very high PEEP and/or FiO<sub>2</sub>, we still believe that ventilator filters should be exchanged with caution to avoid inadvertent lung collapse. Moreover, other brands of ventilators than the one used in this study may have other features, e.g., the auto triggering could be discontinued earlier, and this needs to be considered. Furthermore, other tubing sets with other lengths and

diameters could give other resistance patterns, which could influence the obtained airway pressure.

## Patient position change -time for a new perspective

Many medical procedures involve great safety risks for patients, and these procedures should ideally be preceded by a risk/benefit analysis based on scientific knowledge. Is the change of the endotracheal tube really necessary? If we perform the exchange, what risks are we exposing the patient to? What do we gain with the exchange? And when performing the procedure, probably the whole ward is standing by with help. These procedures are considered to be a risk, because when failing, the outcome can be fatal.

And then there are procedures that are performed worldwide, every day of the week, in most ICU patients that are not considered as patient safety risks due to their basic and simple nature. For example, during sleep, we change body position 20 - 40 times a night, remaining in the same position for an average of 15 min.<sup>93,94</sup> How can a change of the patient's body position possibly be harmful? And the risk of pressure sores is a significant risk in all patients, that is a fact, is it not? Often we make the mistake of applying a certain way of thinking with regard to the critically ill, namely reasoning as in a normal physiological situation, and then applying this line of thinking to the critically ill. For example, when an otherwise healthy person has a viral infection, coughing up airway secretions feels pleasant. Therefore, we sometimes believe that performing endotracheal suctioning will induce the same pleasant feeling in patients. The inherent problem with this way of thinking is that it is applied to two very different situations. On one hand, the normal viral infection with a normal phenomenon that clears the airway and on the other hand a severely pathological situation with tubes, catheters, and drains that is potentially fatal. I believe that the underlying cause is our wish to do good. We want to do as much good as possible, the whole time, and with all patients. This way of thinking in combination with a presumed risk-free procedure that no one remembers when it is implemented and performed on a daily basis, probably explains why some procedures are never questioned.

Frequent change of the patient's position is considered as one of the most important nursing procedures in the ICU. However, although the benefits of this procedure may seem obvious, the scientific support is still limited. The studies usually referred to are often old and performed in a different era when the beds, mattresses, and the overall treatment of the patient were different from current standards. The main indication for changing the patient's body position is to prevent pressure ulcerations.<sup>95-97</sup> In our ICU, the patient is turned every other hour. This 2-hr routine is an accepted international standard,<sup>98,99</sup> but has been questioned due to lack of scientific evidence regarding the frequency of the procedure.<sup>95</sup> With an appropriate pressure redistribu-

tion surface, limited evidence suggests that changing the patient's position every fourth hr is as effective as following the current international standard.<sup>95</sup> The original study of the need for patient position change was performed in a post-operative setting by Chulay and colleagues in 1982.<sup>100</sup> They compared a 2-hr routine with no patient position change during the first 24 hr in 35 post-operative coronary artery bypass patients. The 2-hr routine-group had a significantly shorter period of elevated body temperature as well as a shorter length of stay in the ICU. There were no significant differences between the groups regarding chest radiographic abnormalities or respiratory and circulatory parameters. Notably, the incidence of pressure ulcerations was not measured or reported in this study.

The incidence of pressure ulcerations ranges from 7 to 53% in ICU patients<sup>101,102</sup> and aggressive approaches for prevention, including frequent change of patient position, have been proposed.<sup>97</sup> Nanjo and colleagues<sup>103</sup> have demonstrated that frequent patient position change could instead induce pressure ulcerations by causing sacral skin deformations. On the other hand, a recent study by the Proseva trial group found that a prolonged stay (> 16 hr) in one position, the prone position, is associated with higher incidence of pressure ulcerations.<sup>104</sup> Pressure ulceration probably cause a lot of suffering among our patients. But are there other perspectives to consider when deciding about patient position change? In the third study in this thesis, we found that oxygen desaturation below 90% was the most common serious adverse event and that patient position change caused 28% of the severe desaturations. In studies investigating adverse events during endotracheal intubation, severe hypoxemia is defined as a  $SpO_2 < 80\%$  and hypoxemia as a  $SpO_2 < 90\%$ .<sup>22,23</sup> In our study, 9% of the desaturations would have been regarded as severe hypoxemia with this definition. According to Nunn's oxyhemoglobin dissociation curve<sup>68</sup> (Figure 16), when the  $SpO_2$  is around 80% and the body temperature and pH are normal, the  $PaO_2$  is approximately 6 kPa. An even bigger concern is that a patient with a  $SpO_2 < 80\%$  is on the steep part of the dissociation curve. In this area, even small changes in either oxygen consumption ( $VO_2$ ) (e.g. pain) or oxygen delivery ( $DO_2$ ) (e.g. atelectasis) can have deleterious consequences.

In the light of this, there are many questions needing attention that our study does not answer. How does a short time of hypoxemia affect morbidity and mortality in this patient group? It is probable that in these patients even small changes in, e.g., oxygenation or hemodynamics due to routine care, might induce a vicious cycle deteriorating the patient's condition. In addition, adverse physiologic responses to an intervention may delay detection of signs of important changes in the underlying condition that may require prompt treatment. In fact, knowledge about short episodes of desaturation, hyper- or hypotension, and brady- or tachycardia is limited. In the early stages of hospital care for trauma, just one single drop in blood pressure could indicate a serious worsening of the patient's condition<sup>105</sup> and even increased mortality.<sup>106</sup> This emphasizes the need for adequate monitoring but also that the care related

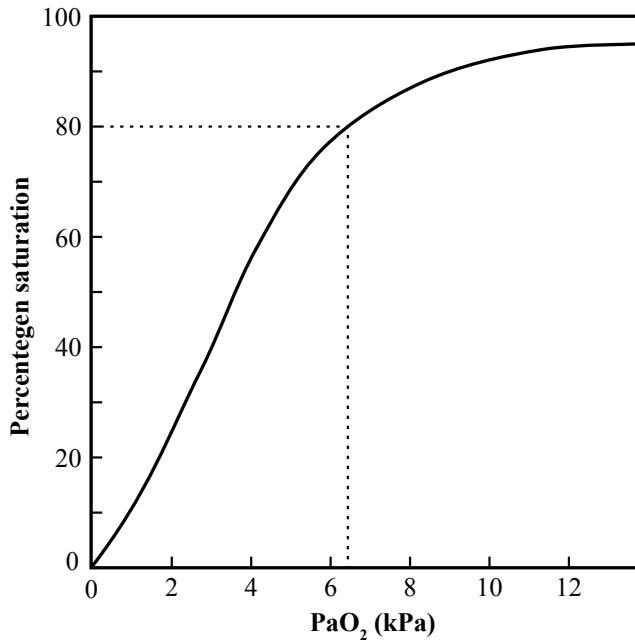


Figure 16. The oxyhaemoglobin dissociation curve.<sup>68</sup>  $PaO_2$  partial pressure of oxygen in arterial blood

to inadvertent physiological responses should be minimized. I think de Jong and colleges<sup>71</sup> have proven an excellent example of a scientific design with regard to finding a serious problem, evaluated what was causing the problem, identifying a preventive method, and then implementing it in clinical practice.

We hypothesized that many patients would become hypoxemic during the endotracheal suctioning maneuver in accordance with previous studies.<sup>30,36,107,108</sup> However, when analyzing the data, we found that endotracheal suctioning was the fifth adverse event generating procedure and that it was not hypoxemia but elevated blood pressure, intensive coughing, and awakening that troubled the patients. In our department, there are written routines regarding endotracheal suctioning that specify the use of a maximum negative suctioning pressure, recommend use of suction support<sup>©</sup> before suctioning, specify the size of the suctioning catheter, and advising that suctioning should be performed with 5 sec cycles and be no longer than 20 to 30 sec in total duration. The adoption of this method is probably at least one explanation why there were few hypoxemic periods correlated with endotracheal suctioning during our study. Moreover, in two of the three occasions where severe blood oxygen desaturation occurred, pre-oxygenation was not performed.

I believe that the de Jong study, the study from Puntillo and colleagues,<sup>109</sup> the study from Vázquez and colleagues<sup>110</sup> and the results of our third study show that patient position change is far more problematic than generally considered. Therefore, recognition of the need of written routines regarding patient position change in the severely critically ill patients is of outmost importance. Questions that need to be addressed are inter alia the frequency of the procedure, how the procedure should be performed to minimize the adverse events, and perhaps whether a dynamic recommendation should be implemented that varies depending on the level of the patients' illness. One suggestion could be to use a color coding scoring system, similar to that used in a study by Hodgson and colleagues.<sup>111</sup> The aim of their study was to develop recommendations on safety parameters for mobilizing mechanically ventilated adults during intensive care. In their study, a green light signifies low risk of an adverse event and that the procedure can usually be performed according to normal protocols and recommendations. A yellow light signifies a potential risk of adverse events, but may be outweighed by the potential benefit of the procedure. A red light signifies a significant risk of adverse events and that the procedure should not be performed if not specifically authorized by the attending intensivist. The implementation of a color coding system in combination with written routines and introduction of a proper pain assessment tool applicable for non-verbal intensive patients may at least be a start of managing a common problem in modern intensive care that potentially can harm our patients.

### If you survive to an ICU, there is a great chance you survive, if you are a trauma patient

The idea for the fourth study in this thesis came directly from our clinical experience in working with traumatically injured patients with pelvis fractures. In our clinical experience, the number of lung complications, especially pulmonary embolism, is high, and many patients suffered from severe hypoxemia in this group of patients during their ICU stay. Therefore we conducted a retrospective registry study and analyzed data from the Uppsala Pelvis database, with 669 patients included between 2003 and 2014. One hundred and twelve patients were included. We found that 1) 67% of the ICU-treated patients had severe respiratory failure, 2) 23 of the ICU treated patients developed severe respiratory failure during the surgical stabilization, and 3) the respiratory failure did not contribute to mortality. Contrary to our gut feeling, we only found pulmonary embolism in 6% of the patients. One explanation for this is that the incidence of pulmonary embolism was not properly explored in all patients, e.g. with CT. Another possible explanation is that we tend to better remember the patients that suffered from pulmonary embolism since they were severely ill and in need of massive efforts from the ICU staff to survive. I especially remember a particular patient that was not included in the study.



He was a young male who suffered major trauma after a car accident. He presented with bilateral femur and a pelvis fractures and subsequently suffered from massive pulmonary embolism. He became so ill that he needed treatment with both NO (nitric oxide) and prone position. During this treatment, a member of the nursing staff wanted to check the patient's pupils an extra time. However, due to the prone position there were obvious difficulties in performing the examination. After some difficulties, we were able to examine the pupils and found that one was dilated. An enormous effort was made to save the patient, but sadly the brain injury was too severe, and his life could not be saved. An autopsy later showed that the cerebral infarction was caused by massive fat embolism. Over the years, I have treated multiple patients with pelvic trauma, but I only remember a few, namely the most critically ill.

Compared to other studies, the incidence of respiratory failure including ARDS in patients with pelvis fractures may seem high. However, we only analyzed the patients treated in the ICU. When using the whole cohort of patients referred to or treated at our hospital as the denominator, the incidence of severe respiratory failure will be 11% and of ARDS 4%. These numbers agree with other studies in unselected patient groups that have reported an incidence of ARDS between 1.5 and 23%.<sup>64,112,113</sup>

We found that lung contusion was associated with the development of respiratory failure after surgical stabilization. This is in line with the findings of Pape and colleagues,<sup>114</sup> who reported that nailing of femur fractures in patients with severe chest trauma was associated with a 33% incidence of ARDS. Likewise, Hoyt and colleagues<sup>55</sup> found a higher incidence of ARDS in patients with chest trauma (20% compared with 3.3% without). We think that it is important to consider not only the surgical procedure that can be "a second hit" and cause deterioration of lung function. In addition, anesthesia and the ventilatory management are important factors in this context. In fact, it has been found that inappropriate ventilation during surgery increases post-operative respiratory complications.<sup>115</sup> Tusman and colleagues<sup>116</sup> have shown that lung complications in patients with lung contusion can be reduced with use of protective ventilation, including low tidal volumes, lung recruitment, and adequate PEEP. Also, in our study, neither adequately high PEEP nor lung recruitment maneuvers were used routinely. Therefore, we believe that a protective ventilatory management during the surgical stabilization could have reduced the high incidence of new respiratory failure in our study.

In contrast to most other studies, early surgical stabilization was associated with the development of new respiratory failure. This finding must be interpreted with caution, because, with the exception of what we discussed above regarding the higher incidence of lung contusion in these patients, this finding can be explained by chance. Furthermore, the respiratory effect of lung contusion may be explained by a time effect independent of the surgical procedure. In the patients who underwent surgery later, lung function did not deteriorate in most cases and even improved in some cases. In addition, this finding was

consider as spurious; it was probably caused by a decision of the orthopedic surgeon to delay the surgical stabilization due to the lung condition, and we cannot know whether the same results would have been obtained if the surgery had been performed earlier. In fact, early surgical stabilization has been found to reduce complications, including ARDS.<sup>63,64,112,113</sup>

Luckily, we found that the mortality rate was low in patients with pelvis fractures, in agreement with other studies.<sup>112,113</sup> Although there were five patients who died in the AHF/ARDS group compared with none in the group without respiratory failure, in no case was it clear that the respiratory condition was a contributing factor. This finding agrees with Treggiari and colleagues,<sup>57</sup> who found that after adjustment for age, ISS, and acute physiological score (APS), there was no association of mortality with ARDS in critically ill trauma patients. Thus, we consider that the respiratory failure is manageable and is not an important cause of death in this patient category.

As stated in the result section, 14% of the patients suffered from trauma that was related to a suicide attempt. When performing this kind of study, many questions regarding the patients' health after the surgery, ICU, and hospital period are raised. From my perspective, if a patient suffers a major trauma (e.g. a fall from a 30-meters radio tower), even if the patient survives, he/she will probably suffer from a low physical functional outcome and thereby a lower quality of life. Borg and colleagues have made several follow-up studies<sup>117-120</sup> in the same patient group that is included in our study. It seems that there is a difference in quality of life between patients depending on the fracture site. Patients with acetabular fractures improve their quality of life over a 2-year period, even though they score lower than a reference population.<sup>119</sup> However, in patients with pelvis ring fractures, patients report a substantially lower quality of life compared with a reference population in both physical and mental domains even at a 2-year follow-up.<sup>118</sup> In a study by Michaels and colleagues<sup>121</sup> in 165 trauma patients, they found that patients with orthopedic injuries had a lower quality of life score compared with patients without orthopedic injuries.

It would be interesting to know how ICU patients with traumatic pelvis fractures compared to non-ICU patients with traumatic pelvis fractures would score in a quality of life study. In surviving ICU patients, the quality of life is significantly lower prior to admission compared to the general population. However, the quality of life improves during a 12-month follow-up but is still lower compared to the general population.<sup>122,123</sup> Remarkably, 43% of the patients did not remember anything from their ICU stay.<sup>123</sup>

# Conclusion

Paper I showed that pharyngeal oxygen administration during apnea at an intubation procedure prevented or considerably increased the time to life-threatening hypoxemia at shunt fractions at least up to 25%. We believe that this technique could be useful in some patients when there is a substantial risk for impaired patient safety, i.e. increased risk for life-threatening hypoxemia. And maybe this technique should be implemented in airway algorithms for the intubation of hypoxemic patients, for example, in the ICU, in the emergency room, in pre-hospital care, and in patients with difficult airways.

Paper II demonstrated that a short disconnection of the expiratory ventilator circuit from the ventilator during filter exchange was not associated with any significant deterioration in lung function. A bench test suggests that this result is explained by auto-triggering with high inspiratory flows during the filter exchange, maintaining the airway pressure.

Paper III showed that adverse events were common, not well documented, and potentially harmful, indicating that it is important to weigh the risk and benefit of routine nursing procedures when caring for circulatory or respiratory unstable critically ill patients.

Paper IV demonstrated that the incidence of respiratory failure in ICU-treated patients with pelvis fractures was high, that the procedure involved in surgical stabilization affected the respiratory status in patients with lung contusion, and that mortality was low and probably not influenced by the respiratory condition.

## Future perspectives

In a future perspective, additional knowledge of the impact on morbidity and mortality of routine nursing procedures, which seems a neglected area, is needed. This knowledge is important both from the patient's perspective and from a scientific point of view. We still do not know how the side effects of routine nursing procedures (e.g. severe coughing, patient/ventilator asynchrony) that are inhibited in only one study arm by, e.g., neuromuscular blockers, could contaminate the results of such studies. Therefore, a larger multi-center study with the aim of investigating this impact would be of great value. This thesis has merely scratched the surface in the field of patient safety. Countless questions are left unanswered.

- What are the indications for certain procedures?
- How often should these procedures be performed?
- What is the scientific knowledge that motivates the particular procedure?
- What do we gain and what do we risk?
- Should all patients be treated the same way? Or have different patients a different need of care? Does this need of care vary during the intensive care period?
- Should care be more individualized (e.g. regarding the changing of the position of the patient) depending on the level of illness? Perhaps some patients should change position more often than today's routine recommends? And with regard to the most severely ill patients that often tend to get even more ill when their position is changed, maybe these patients should have minimal position changes during a limited time frame?

# Acknowledgments

To conduct science, not to mention writing a thesis is a great challenge, with periods of enormous amount of work, sleep deprivation and a reality check that tells you how little you know about everything. But in my opinion, it can be a wonderful journey where you are given the possibility to gain knowledge in areas that you merely could dream of. During this fantastic journey you travel around the world, and meet a lot of warm and devoted people. I have so many to thank for so much. If you read this, you know you matter. To those who have been absolute essential and made my journey possible, my gratitude is expressed in my native tongue.

Min numera något sämre hörande huvudhandledare **Anders Larsson**. Jag är så otroligt tacksam för att du vågade satsa på mig och att du har visat mig en underbar värld. Du har varit en fantastisk handledare och mentor och alltid stötta mig (professionellt som privat). När vi träffades första gången trodde jag inte ens att du visste vem jag var. När du då bjöd in mig att delta i ett forskningsprojekt blev jag otroligt glad. Jag kommer sakna våra resor, våra möten och framförallt den täta kontakten vi haft under slutfasen av min doktorandtid. Jag hade aldrig fått denna möjlighet utan dig, aldrig lärt mig så mycket utan dig och definitivt inte varit den person jag är idag utan dig. Tack för allt Anders!

Min bihandledare, kollega, kompanjon och vän **Henrik Reinius**. Vår resa började 2007, då var jag 24 år, nyexaminerad, nyinflyttad och hade precis fått ett jobb som jag tyckte var otroligt skrämmande. Din förmåga att motivera mig är nästan otäck. Att så många gånger komma till ett möte med känslan att det här kommer faktiskt inte att gå, och lämnat mötet med känslan av att inget kommer vara lättare. Jag kan faktiskt inte beskriva hur tacksam jag är för att fått möjligheten att lära känna dig. Tack Henrik för att du lärt mig att våga tro på mig själv, att stå upp för de saker som jag tror på, för att du hjälpt mig när botten inte var långt borta och för att du visat vad som är viktigt i livet. Den här boken hade aldrig påbörjats, än mindre slutförts utan din heroiska insats.

Min bihandledare **Camilla Fröjd**, tack för att du gav mig möjligheten att forska och allt du bidragit med.

Min skidåkar-, gymnasie- sjuksköterske-, specialistsjuksköterske-, filmskapar-, forskar-, båtägar- och resvän **Erik Bruno**. Lite galet är det faktiskt när jag

tänker tillbaka på allt vi åstadkommit. Jag har så mycket att tacka dig för Erik. Tack!

Till den mest talangfulle personen jag någonsin träffat. Tack **Viktor Erbring** för att du alltid funnits där när jag som mest behövt dig.

Min polisiära skidåknings-vän **Lars Lundberg**. Tack för alla de timmar vi ägnat tillsammans och för att du lärt mig att en stark vilja kan åstadkomma underverk.

Tack **Hans Jonsson** för alla träningstimmar, för all undervisning och djupgående diskussioner.

Tack **Staffan Høstman** för hjälpen med precis allt på labbet, i Debian, i Netbeans, i Java och för att du alltid har tid för mig, trots att jag vet att du inte har det.

Tack **Janne Juoperi** för att du alltid säger sanningen, inte backar och för att du tror på mig.

Mina rumskamrater **Ing-Marie Larsson** och **Ewa Wallin**. Undrar vad jag skulle gjort utan möjligheten att ställa massor av dumma frågor. Tack för stötningen och att jag fått chansen att undervisa.

Min CIVA- och doktorandkollega **Anna Aronsson**. Tack för att du väckte mitt intresse för respiration och att jag fick chansen att arbeta i respgruppen. Du står på tur!

Tack **Vänner och kollegor på CIVA** för att ni stått ut med alla mina projekt och för att ni alltid frågar hur det är.

Till **Tjocka släkten och mina vänner** för att ni inte är kloka och aldrig slutar förvåna mig.

Tack **Morbror Lars** för introduktionen till datorer och prylar. Du väckte mitt intresse och lade grunden till all min tekniska kunskap jag har idag. En kunskap som hjälpt mig mycket i min profession och i min forskning.

Tack kära svärmor **Ingrid Wågström** för all hjälp och stöttning under alla dessa år.

Min käre svärfar **Göran Wågström** som visat mig konsten att laga fantastisk mat och hur man får kolonilotten att grönska. Tack för allt du gör för

mig!

Tack **Pappa** för att du alltid motiverat mig att göra mitt bästa. För att du fått mig att inse glädjen i att hårt arbete, i fysisk aktivitet och att ta hand om kroppen. Utan dina goda råd och din hjälp hade jag aldrig blivit sjuksköterska, aldrig läst vidareutbildning och aldrig haft de möjligheter jag har idag.

Min underbara **Mamma** som inte fick läsa detta. Som inte fick delta på min disputation eller på festen. Som inte fick se Hjalmar växa upp. Tack för den unika person du var och för allt du lärt mig. Jag kommer alltid sakna dig!

Tack **Hjalmar** för alla härliga stunder du ger mig och för att du är precis den du är. Vår resa har bara börjat och den kommer bli skitkul!

Mitt livs kärlek **Kajsa**. Tack för att du står ut med min arbetsnarkomani, min städfascism i köket och för att du tror att jag kan göra saker som jag inte själv tror. Du är fantastisk!

# References

1. Hornabrook RW. The Safety Of Ethyl Chloride, And The Position Of The Patient During General Anaesthesia. *British Medical Journal*. 1929; 1(3558):500.
2. Moyen E, Camiré E and Stelfox HT. Clinical review: Medication errors in critical care. *Critical Care*. 2008; 12(2):208.
3. Rothschild JM, Landrigan CP, Cronin JW, Kaushal R, Lockley SW, Burdick E, Stone PH, Lilly CM, Katz JT and Czeisler CA. The Critical Care Safety Study: The incidence and nature of adverse events and serious medical errors in intensive care\*. *Critical Care Medicine*. 2005; 33(8):1694.
4. Landrigan CP, Parry GJ, Bones CB, Hackbarth AD, Goldmann DA and Sharek PJ. Temporal trends in rates of patient harm resulting from medical care. *New England Journal of Medicine*. 2010; 363(22):2124–2134.
5. Longo DR, Hewett JE, Ge B and Schubert S. The long road to patient safety. *JAMA: the journal of the American Medical Association*. 2005; 294(22):2858–2865.
6. Merino P, Álvarez J, Martín MC, Alonso Á and Gutiérrez I. Adverse events in Spanish intensive care units: the SYREC study. *International Journal for Quality in Health Care*. 2011; .
7. Schmittinger CA, Torgersen C, Luckner G, Schröder DCH, Lorenz I and Dünser MW. Adverse cardiac events during catecholamine vasopressor therapy: a prospective observational study. *Intensive Care Medicine*. 2012; 38(6):950–958.
8. Stockwell DC and Slonim AD. Quality and safety in the intensive care unit. *Journal of Intensive Care Medicine*. 2006; 21:199–210.
9. Valentín A, Capuzzo M, Guidet B, Moreno R, Metnitz B, Bauer P and Metnitz P. Errors in administration of parenteral drugs in intensive care units: multinational prospective study. *BMJ: British Medical Journal*. 2009; 338.
10. Welters ID, Gibson J, Mogk M and Wenstone R. Major sources of critical incidents in intensive care. *Critical Care*. 2011; 15(5):R232.
11. Kohn LT, Corrigan JM and Donaldson MS. *To Err is Human: Building a Safer Health System*. 2000. ISBN 0309068371.
12. Hayward RA and Hofer TP. Estimating hospital deaths due to medical errors: preventability is in the eye of the reviewer. *JAMA*. 2001; 286(4):415–20.
13. Leape LL. Institute of Medicine medical error figures are not exaggerated. *JAMA*. 2000; 284(1):95–7.
14. Nuckols TK, Bell DS, Liu H, Paddock SM and Hilborne LH. Rates and types of events reported to established incident reporting systems in two US hospitals. *Qual Saf Health Care*. 2007; 16:164–168.
15. Milch CE, Salem DN, Pauker SG, Lundquist TG, Kumar S and Chen J. Voluntary electronic reporting of medical errors and adverse events. An analysis



- of 92,547 reports from 26 acute care hospitals. *Journal of General Internal Medicine*. 2006; 21:165–170.
16. Orgeas MG, Timsit JF, Soufir L, Tafflet M, Adrie C, Philippart F, Zahar JR, Clech C, Goldran-Toledano D and Jamali S. Impact of adverse events on outcomes in intensive care unit patients\*. *Critical Care Medicine*. 2008; 36(7):2041–2047.
  17. Graf J, Von den Driesch A, Koch K and Janssens U. Identification and characterization of errors and incidents in a medical intensive care unit. *Acta Anaesthesiologica Scandinavica*. 2005; 49(7):930–939.
  18. Valentin A, Capuzzo M, Guidet B, Moreno RP, Dolanski L, Bauer P and Metnitz PGH. Patient safety in intensive care: Results from the multinational Sentinel Events Evaluation (SEE) study. *Intensive Care Medicine*. 2006; 32(10):1591–1598.
  19. Mort TC. Emergency Tracheal Intubation: Complications Associated with Repeated Laryngoscopic Attempts. *Anesthesia & Analgesia*. 2004; 99(2):607–613.
  20. Brismar B, Hedenstierna G, Lundquist H, Strandberg A, Svensson L and Tokics L. Pulmonary densities during anesthesia with muscular relaxation—a proposal of atelectasis. *Anesthesiology*. 1985; 62(4):422–428.
  21. Schwartz DE, Matthay MA and Cohen NH. Death and other complications of emergency airway management in critically ill adults: A prospective investigation of 297 tracheal intubations. *Anesthesiology*. 1995; 82(2):367.
  22. Griesdale DEG, Bosma TL, Kurth T, Isac G and Chittock DR. Complications of endotracheal intubation in the critically ill. *Intensive care medicine*. 2008; 34(10):1835–42.
  23. Jaber S. Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Critical Care Medicine*. 2006; 34(9):2355–2361.
  24. Hasegawa K, Shigemitsu K, Hagiwara Y, Chiba T, Watase H, Brown CA and Brown DFM. Association between repeated intubation attempts and adverse events in emergency departments: an analysis of a multicenter prospective observational study. *Annals of Emergency Medicine*. 2012; .
  25. Benumof JL. Preoxygenation: best method for both efficacy and efficiency? *Anesthesiology*. 1999; 91(3):603.
  26. Mort TC. Preoxygenation in critically ill patients requiring emergency tracheal intubation\*. *Critical Care Medicine*. 2005; 33(11):2672.
  27. Baillard C, Fosse JP, Sebbane M, Chanques G, Vincent F, Courouble P, Cohen Y, Eledjam JJ, Adnet F and Jaber S. Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. *American Journal of Respiratory and Critical Care Medicine*. 2006; 174(2):171.
  28. Delay JM, Sebbane M, Jung B, Nocca D, Verzilli D, Pouzeratte Y, Kamel ME, Fabre JM, Eledjam JJ and Jaber S. The effectiveness of noninvasive positive pressure ventilation to enhance preoxygenation in morbidly obese patients: a randomized controlled study. *Anesthesia and Analgesia*. 2008; 107(5):1707.
  29. Celebi S, Koner O, Menda F, Omay O, Gunay I, Suzer K and Cakar N. Pulmonary effects of noninvasive ventilation combined with the recruitment maneuver after cardiac surgery. *Anesthesia and Analgesia*. 2008;

- 107(2):614–619.
30. Dyrh T, Bonde J and Larsson A. Lung recruitment manoeuvres are effective in regaining lung volume and oxygenation after open endotracheal suctioning in acute respiratory distress syndrome. *Critical care*. 2002; 7(1):55.
  31. Diaz JV, Brower R, Calfee CS and Matthay MA. Therapeutic strategies for severe acute lung injury. *Critical Care Medicine*. 2010; 38(8):1644.
  32. Pinhu L, Whitehead T, Evans T and Griffiths M. Ventilator-associated lung injury. *Lancet*. 2003; 361(9354):332–340.
  33. Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. *New England Journal of Medicine*. 2000; 342(18):1301–1308.
  34. De Campo T and Civetta JM. The effect of short-term discontinuation of high-level PEEP in patients with acute respiratory failure. *Critical Care Medicine*. 1979; 7(2):47–49.
  35. Neumann P, Berglund JE, Fernandez Mondejar E, Magnusson A and Hedenstierna G. Dynamics of lung collapse and recruitment during prolonged breathing in porcine lung injury. *Journal of Applied Physiology*. 1998; 85(4):1533–1543.
  36. Lindgren S, Odenstedt H, Olegård C, Söndergaard S, Lundin S and Stenqvist O. Regional lung derecruitment after endotracheal suction during volume-or pressure-controlled ventilation: a study using electric impedance tomography. *Intensive Care Medicine*. 2007; 33(1):172–180.
  37. Amato MBP, Barbas CSV, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C and Oliveira R. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *New England Journal of Medicine*. 1998; 338(6):347.
  38. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ and Stewart TE. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 2008; 299(6):637–645.
  39. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R and Bugeo G. Lung recruitment in patients with the acute respiratory distress syndrome. *New England Journal of Medicine*. 2006; 354(17):1775–1786.
  40. Fan E, Wilcox ME, Brower RG, Stewart TE, Mehta S, Lapinsky SE, Meade MO and Ferguson ND. Recruitment maneuvers for acute lung injury: a systematic review. *American Journal of Respiratory and Critical Care Medicine*. 2008; 178(11):1156–1163.
  41. Gattinoni L, D’Andrea L, Pelosi P, Vitale G, Pesenti A and Fumagalli R. Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome. *JAMA*. 1993; 269(16):2122–2127.
  42. Neumann P, Rothen HU, Berglund JE, Valtysson J, Magnusson A and Hedenstierna G. Positive end-expiratory pressure prevents atelectasis during general anaesthesia even in the presence of a high inspired oxygen concentration. *Acta Anaesthesiologica Scandinavica*. 1999; 43(3):295–301.

43. Rothen HU, Sporre B, Engberg G, Wegenius G and Hedenstierna G. Airway closure, atelectasis and gas exchange during general anaesthesia. *British Journal of Anaesthesia*. 1998; 81(5):681–686.
44. Tokics L, Hedenstierna G, Strandberg A, Brismar BO and Lundquist H. Lung collapse and gas exchange during general anesthesia: effects of spontaneous breathing, muscle paralysis, and positive end-expiratory pressure. *Anesthesiology*. 1987; 66(2):157.
45. Gunnarsson L, Strandberg A, Brismar B, Tokics L, Lundquist H and Hedenstierna G. Atelectasis and gas exchange impairment during enflurane/nitrous oxide anaesthesia. *Acta Anaesthesiologica Scandinavica*. 1989; 33(8):629–637.
46. Rothen HU, Sporre B, Engberg G, Wegenius G, Reber A and Hedenstierna G. Prevention of atelectasis during general anaesthesia. *Lancet*. 1995; 345(8962):1387–1391.
47. Rehder K, Hatch DJ, Sessler AD and Fowler WS. The function of each lung of anesthetized and paralyzed man during mechanical ventilation. *Anesthesiology*. 1972; 37(1):16–26.
48. Eichenberger AS, Proietti S, Wicky S, Frascarolo P, Suter M, Spahn DR and Magnusson L. Morbid obesity and postoperative pulmonary atelectasis: an underestimated problem. *Anesthesia and analgesia*. 2002; 95(6):1788–1792.
49. Pelosi P, Croci M, Ravagnan I, Tredici S, Pedoto A, Lissoni A and Gattinoni L. The effects of body mass on lung volumes, respiratory mechanics, and gas exchange during general anesthesia. *Anesthesia and Analgesia*. 1998; 87(3):654–660.
50. Reinius H, Jonsson L, Gustafsson S, Sundbom M, Duvernoy O, Pelosi P, Hedenstierna G and Fredén F. Prevention of Atelectasis in Morbidly Obese Patients during General Anesthesia and Paralysis: A Computerized Tomography Study. *Anesthesiology*. 2009; 111(5):979.
51. Benidixen HH, Hedley-Whyte J and Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. A concept of atelectasis. *Survey of Anesthesiology*. 1964; 8(6):571.
52. Mead J and Collier C. Relation of volume history of lungs to respiratory mechanics in anesthetized dogs. *Journal of Applied Physiology*. 1959; 14(5):669–678.
53. Benumof JL. Mechanism of decreased blood flow to atelectatic lung. *Journal of Applied Physiology*. 1979; 46(6):1047–1048.
54. Barer GR, Howard P, McCurrie JR and Shaw JW. Changes in the pulmonary circulation after bronchial occlusion in anesthetized dogs and cats. *Circulation Research*. 1969; 25(6):747–764.
55. Hoyt DB, Simons RK, Winchell RJ, Cushman J, Hollingsworth-Fridlund P, Holbrook T and Fortlage D. A risk analysis of pulmonary complications following major trauma. *Journal of Trauma and Acute Care Surgery*. 1993; 35(4):524–531.
56. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ and Hudson LD. Incidence and outcomes of acute lung injury. *New England Journal of Medicine*. 2005; 353(16):1685–1693.
57. Treggiari MM, Hudson LD, Martin DP, Weiss NS, Caldwell E and Rubenfeld G.

- Effect of acute lung injury and acute respiratory distress syndrome on outcome in critically ill trauma patients. *Critical Care Medicine*. 2004; 32(2):327–331.
58. Miller PR, Croce MA, Kilgo PD, Scott J and Fabian TC. Acute respiratory distress syndrome in blunt trauma: identification of independent risk factors. *The American surgeon*. 2002; 68(10):845–50; discussion 850–1.
  59. Watkins TR, Nathens AB, Cooke CR, Psaty BM, Maier RV, Cuschieri J and Rubenfeld GD. Acute respiratory distress syndrome after trauma: development and validation of a predictive model. *Critical Care Medicine*. 2012; 40(8):2295–2303.
  60. Hudson LD, Milberg JA, Anardi D and Maunder RJ. Clinical risks for development of the acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*. 1995; 151(2 Pt 1):293–301.
  61. Lefaivre KA, Starr AJ, Stahel PF, Elliott AC and Smith WR. Prediction of pulmonary morbidity and mortality in patients with femur fracture. *Journal of Trauma and Acute Care Surgery*. 2010; 69(6):1527–1536.
  62. Kanakaris NK, Angoules AG, Nikolaou VS, Kontakis G and Giannoudis PV. Treatment and outcomes of pelvic malunions and nonunions: a systematic review. *Clinical Orthopaedics and Related Research*®. 2009; 467(8):2112–2124.
  63. Nahm NJ and Vallier HA. Timing of definitive treatment of femoral shaft fractures in patients with multiple injuries. *Journal of Trauma and Acute Care Surgery*. 2012; 73(5):1046–1063.
  64. Vallier HA, Cureton BA, Ekstein C, Oldenburg FP and Wilber JH. Early Definitive Stabilization of Unstable Pelvis and Acetabulum Fractures Reduces Morbidity. *The Journal of Trauma: Injury, Infection, and Critical Care*. 2010; 69(3):677–684.
  65. Valta P, Uusaro A, Nunes S, Ruokonen E and Takala J. Acute respiratory distress syndrome: frequency, clinical course, and costs of care. *Critical Care Medicine*. 1999; 27(11):2367–2374.
  66. Phua J, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, Scales DC, Stather DR, Li A, Jones A, Gattas DJ, Hallett D, Tomlinson G, Stewart TE and Ferguson ND. Has mortality from acute respiratory distress syndrome decreased over time?: A systematic review. *American Journal of Respiratory and Critical Care Medicine*. 2009; 179(3):220–227.
  67. Salim A, Martin M, Constantinou C, Sangthong B, Brown C, Kasotakis G, Demetriades D and Belzberg H. Acute respiratory distress syndrome in the trauma intensive care unit: morbid but not mortal. *Archives of Surgery*. 2006; 141(7):655–658.
  68. Lumb A. *Nunn's Applied Respiratory Physiology*. Butterworth-Heinemann, 6 edition. 2005. ISBN 0750687916.
  69. User's manual Ventilator system Servo-i V3.0 - Maquet.
  70. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP and Elswick RK. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *American journal of respiratory and critical care medicine*. 2002; 166(10):1338–44.
  71. de Jong A, Molinari N, de Lattre S, Gniadek C, Carr J, Conseil M, Susbielles MP, Jung B, Jaber S and Chanques G. Decreasing severe pain and serious

- adverse events while moving intensive care unit patients: a prospective interventional study (the NURSE-DO project). *Critical care*. 2013; 17(2):R74.
72. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L and Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012; 307(23):2526–2533.
  73. Engström J, Hedenstierna G and Larsson A. Pharyngeal oxygen administration increases the time to serious desaturation at intubation in acute lung injury: An experimental study. *Critical Care*. 2010; 14(3).
  74. Draper WB and Whitehead RW. Diffusion Respiration in the Dog Anesthetized By Eentothal Sodium. *Anesthesiology*. 1944; 5(3):262.
  75. Enghoff H. Diffusion respiration in man. *Nature*. 1951; (168):830.
  76. Holmdahl MH. Pulmonary uptake of oxygen, acid-base metabolism, and circulation during prolonged apnoea. *Acta Chirurgica Scandinavica. Supplementum*. 1956; 212:1.
  77. Frumin M, Epstein RM and Cohen G. Apneic oxygenation in man. *Anesthesiology*. 1959; 20(6):789.
  78. Teller LE, Alexander CM, Frumin MJ and Gross JB. Pharyngeal insufflation of oxygen prevents arterial desaturation during apnea. *Anesthesiology*. 1988; 69(6):980.
  79. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*. 2003; 98(5):1269–1277.
  80. Cook T, Woodall N and Frerk C. Major complications of airway management in the United Kingdom. *National Audit Project*. 2011; 4.
  81. Helm M, Kremers G, Lampl L and Hossfeld B. Incidence of transient hypoxia during pre-hospital rapid sequence intubation by anaesthesiologists. *Acta Anaesthesiologica Scandinavica*. 2013; 57(2):199–205.
  82. Rosenstock C, Møller J and Hauberg A. Complaints related to respiratory events in anaesthesia and intensive care medicine from 1994 to 1998 in Denmark. *Acta Anaesthesiologica Scandinavica*. 2001; 45(1):53–58.
  83. Lampland AL, Plumm B, Meyers PA, Worwa CT and Mammel MC. Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure. *The Journal of pediatrics*. 2009; 154(2):177–182. e2.
  84. Parke R, McGuinness S and Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. *British Journal of Anaesthesia*. 2009; 103(6):886.
  85. Groves N and Tobin A. High flow nasal oxygen generates positive airway pressure in adult volunteers. *Australian Critical Care*. 2007; 20(4):126–131.
  86. Engström J, Reinius H, Hedenstierna G and Larsson A. Nasal high flow oxygen administration might be risky in conjunction with endotracheal intubation. *Intensive Care Medicine*. 2011; 37:S93.
  87. Semler MW, Janz DR, Lentz RJ, Matthews DT, Norman BC, Assad TR, Keriwala RD, Ferrell BA, Noto MJ, McKown AC, Kocurek EG, Warren MA, Huerta LE and Rice TW. Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill. *American journal of respiratory and critical care medicine*. 2015; 193(3):273–80.

88. Wimalasena Y, Burns B, Reid C, Ware S and Habig K. Apneic oxygenation was associated with decreased desaturation rates during rapid sequence intubation by an Australian helicopter emergency medicine service. *Annals of emergency medicine*. 2015; 65(4):371–6.
89. Miguel-Montanes R, Hajage D, Messika J, Bertrand F, Gaudry S, Rafat C, Labbé V, Dufour N, Jean-Baptiste S, Bedet A, Dreyfuss D and Ricard JD. Use of high-flow nasal cannula oxygen therapy to prevent desaturation during tracheal intubation of intensive care patients with mild-to-moderate hypoxemia. *Critical care medicine*. 2015; 43(3):574–83.
90. Patel A and Nouraei SAR. Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. *Anaesthesia*. 2015; 70(3):323–9.
91. Sakles JC, Mosier JM, Patanwala AE and Dicken JM. Apneic oxygenation is associated with a reduction in the incidence of hypoxemia during the RSI of patients with intracranial hemorrhage in the emergency department. *Internal and emergency medicine*. 2016; .
92. Engström J, Reinius H, Fröjd C, Jonsson H, Hedenstierna G and Larsson A. Maintenance of airway pressure during filter exchange due to Auto-Trigging. *Respiratory Care*. 2014; 59(8):1210–1217.
93. Gordon S, Grimmer K and Trott P. Self-reported versus recorded sleep position: an observational study. *Internet Journal of Allied . . .* 2004; .
94. De Koninck J, Gagnon P and Lallier S. Sleep positions in the young adult and their relationship with the subjective quality of sleep. *Sleep*. 1983; 6(1):52–9.
95. Krapfl LA and Gray M. Does regular repositioning prevent pressure ulcers? *Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society / WOCN*. 2008; 35(6):571–7.
96. Cox J. Predictors of Pressure Ulcers in Adult Critical Care Patients. *American Journal of Critical Care*. 2011; 20(5):364–375.
97. Knox DM, Anderson TM and Anderson PS. Effects of different turn intervals on skin of healthy older adults. *Advances in wound care : the journal for prevention and healing*. 1994; 7(1):48–52, 54–6.
98. Krishnagopalan S, Johnson EW, Low LL and Kaufman LJ. Body positioning of intensive care patients: clinical practice versus standards. *Critical care medicine*. 2002; 30(11):2588–92.
99. Goldhill DR, Badacsonyi A, Goldhill AA and Waldmann C. A prospective observational study of ICU patient position and frequency of turning. *Anaesthesia*. 2008; 63(5):509–15.
100. Chulay M, Brown J and Summer W. Effect of postoperative immobilization after coronary artery bypass surgery. *Critical care medicine*. 1982; 10(3):176–9.
101. Whittington KT and Briones R. National Prevalence and Incidence Study: 6-year sequential acute care data. *Advances in skin & wound care*. 2004; 17(9):490–4.
102. Schuurman JP, Schoonhoven L, Keller BPJA and van Ramshorst B. Do pressure ulcers influence length of hospital stay in surgical cardiothoracic patients? A prospective evaluation. *Journal of clinical nursing*. 2009; 18(17):2456–63.
103. Nanjo Y, Nakagami G, Kaitani T, Naito A, Takehara K, Lijuan J, Yahagi N and Sanada H. Relationship between morphological characteristics and etiology of

- pressure ulcers in intensive care unit patients. *Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society / WOCN*. 2011; 38(4):404–12.
104. Girard R, Baboi L, Ayzac L, Richard JC and Guérin C. The impact of patient positioning on pressure ulcers in patients with severe ARDS: results from a multicentre randomised controlled trial on prone positioning. *Intensive care medicine*. 2014; 40(3):397–403.
  105. Seamon MJ, Feather C, Smith BP, Kulp H, Gaughan JP and Goldberg AJ. Just one drop: the significance of a single hypotensive blood pressure reading during trauma resuscitations. *The Journal of trauma*. 2010; 68(6):1289.
  106. Zenati MS, Billiar TR, Townsend RN, Peitzman AB and Harbrecht BG. A brief episode of hypotension increases mortality in critically ill trauma patients. *The Journal of trauma*. 2002; 53(2):232.
  107. Dyhr T, Laursen N and Larsson A. Effects of lung recruitment maneuver and positive end-expiratory pressure on lung volume, respiratory mechanics and alveolar gas mixing in patients ventilated after cardiac surgery. *Acta Anaesthesiologica Scandinavica*. 2002; 46(6):717–725.
  108. Pedersen CM, Rosendahl-Nielsen M, Hjermand J and Egerod I. Endotracheal suctioning of the adult intubated patient—What is the evidence? *Intensive and Critical Care Nursing*. 2009; 25(1):21–30.
  109. Puntillo KA, Morris AB, Thompson CL, Stanik-Hutt J, White CA and Wild LR. Pain behaviors observed during six common procedures: results from Thunder Project II. *Critical care medicine*. 2004; 32(2):421–7.
  110. Vázquez M, Pardavila MI, Lucia M, Aguado Y, Margall MÁ and Asiain MC. Pain assessment in turning procedures for patients with invasive mechanical ventilation. *Nursing in critical care*; 16(4):178–85.
  111. Hodgson CL, Stiller K, Needham DM, Tipping CJ, Harrold M, Baldwin CE, Bradley S, Berney S, Caruana LR, Elliott D, Green M, Haines K, Higgins AM, Kaukonen KM, Leditschke I, Nickels MR, Paratz J, Patman S, Skinner EH, Young PJ, Zanni JM, Denehy L and Webb SA. Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. *Critical Care*. 2014; 18(6):658.
  112. Vallier HA, Super DM, Moore TA and Wilber JH. Do patients with multiple system injury benefit from early fixation of unstable axial fractures? The effects of timing of surgery on initial hospital course. *Journal of orthopaedic trauma*. 2013; 27(7):405–12.
  113. Vallier HA, Moore TA, Como JJ, Wilczewski PA, Steinmetz MP, Wagner KG, Smith CE, Wang XF and Dolenc AJ. Complications are reduced with a protocol to standardize timing of fixation based on response to resuscitation. *Journal of orthopaedic surgery and research*. 2015; 10:155.
  114. Pape HC, Regel G, Dwenger A, Sturm JA and Tscherne H. Influence of thoracic trauma and primary femoral intramedullary nailing on the incidence of ARDS in multiple trauma patients. *Injury*. 1993; 24 Suppl 3:S82–103.
  115. Ladha K, Vidal Melo MF, McLean DJ, Wanderer JP, Grabitz SD, Kurth T and Eikermann M. Intraoperative protective mechanical ventilation and risk of postoperative respiratory complications: hospital based registry study. *BMJ (Clinical research ed.)*. 2015; 351:h3646.

116. Tusman G, Böhm SH, Warner DO and Sprung J. Atelectasis and perioperative pulmonary complications in high-risk patients. *Current opinion in anaesthesiology*. 2012; 25(1):1–10.
117. Borg T, Holstad M and Larsson S. Quality of life in patients operated for pelvic fractures caused by suicide attempt by jumping. *Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society*. 2010; 99(3):180–6.
118. Borg T, Berg P, Fugl-Meyer K and Larsson S. Health-related quality of life and life satisfaction in patients following surgically treated pelvic ring fractures. A prospective observational study with two years follow-up. *Injury*. 2010; 41(4):400–4.
119. Borg T, Berg P and Larsson S. Quality of life after operative fixation of displaced acetabular fractures. *Journal of orthopaedic trauma*. 2012; 26(8):445–50.
120. Borg T and Hailer NP. Outcome 5 years after surgical treatment of acetabular fractures: a prospective clinical and radiographic follow-up of 101 patients. *Archives of orthopaedic and trauma surgery*. 2015; 135(2):227–33.
121. Michaels AJ, Madey SM, Krieg JC and Long WB. Traditional injury scoring underestimates the relative consequences of orthopedic injury. *The Journal of trauma*. 2001; 50(3):389–95; discussion 396.
122. Dowdy DW, Eid MP, Sedrakyan A, Mendez-Tellez PA, Pronovost PJ, Herridge MS and Needham DM. Quality of life in adult survivors of critical illness: a systematic review of the literature. *Intensive care medicine*. 2005; 31(5):611–20.
123. Kvåle R, Ulvik A and Flaatten H. Follow-up after intensive care: a single center study. *Intensive care medicine*. 2003; 29(12):2149–56.





# Acta Universitatis Upsaliensis

*Digital Comprehensive Summaries of Uppsala Dissertations  
from the Faculty of Medicine 1187*

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title "Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine".)

Distribution: [publications.uu.se](http://publications.uu.se)  
urn:nbn:se:uu:diva-275170



ACTA  
UNIVERSITATIS  
UPSALIENSIS  
UPPSALA  
2016