Benefits of Spontaneous Breathing

Compared with Mechanical Ventilation

LÁSZLÓ VIMLÁTI
Abstract


When spontaneous breathing (SB) is allowed during mechanical ventilation (MV), atelectatic lung areas are recruited and oxygenation improves thereby. Whether unsupported SB at its natural pattern (without PEEP and at low pressure/small tidal volume) equally recruits and improves oxygenation, and if so by which mechanism, has not been studied.

A porcine lung collapse model was designed to study this question. The cardiac output dependency of the pulmonary shunt was investigated with healthy lungs and with major shunt (during one-lung ventilation) and with SB, MV and continuous positive airway pressure (CPAP). The hypoxic pulmonary vasoconstriction (HPV) was blocked with sodium nitroprusside (SNP) to see whether HPV is the only mechanism available for ventilation/perfusion (VA/Q) matching during MV and SB. In all experiments, respiratory rate and tidal volume during MV were matched to SB. Oxygenation was assessed by serial blood gas measurements, recruitment by thoracic CTs; pulmonary shunt was assessed by multiple inert gas elimination or venous admixture.

SB attained better oxygenation and lower pulmonary shunt compared with MV, although it did not recruit collapsed lung. Pulmonary shunt did not correlate with cardiac output during SB, whereas a correlation was found during MV and CPAP. With blocked HPV, pulmonary shunt was considerably lower during SB than MV.

In conclusion, SB improves VA/Q matching as compared with MV, even when no recruitment occurs. In contrast to MV and CPAP, cardiac output has no major effect on pulmonary shunt during SB. The improved VA/Q matching during SB despite a blocked HPV might indicate the presence of a SB-specific mechanism that improves pulmonary blood flow redistribution towards ventilated lung regions independent of or supplementary to HPV.

Keywords: spontaneous breathing, mechanical ventilation, pulmonary shunt, oxygenation, hypoxic pulmonary vasoconstriction

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To my loving family – who made it possible,

and to my late father – who made it necessary.
List of Papers

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


III Vimlati L, Larsson A, Hedenstierna G, Lichtwarck-Aschoff M Pulmonary shunt is independent of decrease in cardiac output during unsupported spontaneous breathing in the pig. (submitted)

IV Vimlati L, Larsson A, Hedenstierna G, Lichtwarck-Aschoff M Spontaneous breathing reduces pulmonary shunt independent of hypoxic vasoconstriction in the lung collapse model. (manuscript)

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## Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ALI</td>
<td>acute lung injury</td>
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<tr>
<td>APRV</td>
<td>airway pressure release ventilation</td>
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<td>ARDS</td>
<td>acute respiratory distress syndrome</td>
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<tr>
<td>BiPAP</td>
<td>bi-level positive airway pressure</td>
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<tr>
<td>CO</td>
<td>cardiac output</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>FiO₂</td>
<td>fraction of inspired oxygen</td>
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<tr>
<td>HPV</td>
<td>hypoxic pulmonary vasoconstriction</td>
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<tr>
<td>HU</td>
<td>Hounsfield unit</td>
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<td>MIGET</td>
<td>multiple inert gas elimination technique</td>
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<tr>
<td>mPAP</td>
<td>mean pulmonary artery pressure</td>
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<td>MV</td>
<td>mechanical ventilation</td>
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<td>NPA</td>
<td>negative pressure application</td>
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<tr>
<td>OLV</td>
<td>one-lung ventilation</td>
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<tr>
<td>PaO₂</td>
<td>arterial partial pressure of oxygen</td>
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<tr>
<td>PAO₂</td>
<td>alveolar partial pressure of oxygen</td>
</tr>
<tr>
<td>Paw</td>
<td>airway pressure</td>
</tr>
<tr>
<td>Pₚₚₜₜm</td>
<td>pulmonary perfusion pressure</td>
</tr>
<tr>
<td>PV(O₂)</td>
<td>mixed-venous partial pressure of oxygen</td>
</tr>
<tr>
<td>PEEP</td>
<td>positive end-expiratory pressure</td>
</tr>
<tr>
<td>Qv/Q̇t</td>
<td>venous admixture</td>
</tr>
<tr>
<td>R²</td>
<td>coefficient of determination</td>
</tr>
<tr>
<td>RR</td>
<td>respiratory rate</td>
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<tr>
<td>SB</td>
<td>spontaneous breathing</td>
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<tr>
<td>SNP</td>
<td>sodium nitroprusside</td>
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<tr>
<td>VA/Q (mis)match</td>
<td>alveolar ventilation/perfusion (mis)match</td>
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<tr>
<td>V_T</td>
<td>tidal volume</td>
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At first glance, to ask why spontaneous breathing would be beneficial or “better” than mechanical ventilation might seem an odd question.

Respiratory support is provided when spontaneous breathing (SB) is insufficient to maintain adequate oxygenation and/or carbon dioxide removal. Lung pathology causing a ventilation/perfusion mismatch including acute lung injury (ALI) or adult respiratory distress syndrome (ARDS), chest wall dysfunction as with rib fractures or pneumothorax, respiratory muscle fatigue, neural dysfunction e.g. respiratory depression. Mechanical ventilation (MV), the form of respiratory support used most often, is undeniably extremely effective in saving lives.

On the other hand, over millions of years of evolution, mammalian lungs have developed/adapted to master the gas exchange during spontaneous breathing, and the same construct might not be that optimal when being ventilated with a respirator using positive pressure.

Only for some decades ago, blinded by its remarkable short-term effectiveness, physicians implicitly believed that mechanical ventilation was superior to spontaneous breathing, to the point that a patient on the ventilator trying to take his or her own breaths was regarded as “fighting the ventilator” and those efforts were quickly silenced with muscle relaxants. To question whether any potential injury could be induced by mechanical ventilation was non-sense, despite, for example, a high incidence of pneumothorax. Apart for a handful of researchers like Civetta, Kirby and Downs, few could perceive any benefit at all in spontaneous breathing over mechanical ventilation at that time.

Together with awareness of ventilator-induced lung injury, the interest in modes of ventilation that allow for or augment spontaneous breathing is now growing. New questions arise; perhaps because the old ones about how, precisely, SB works have not been answered satisfactorily.
Introduction

Concern is growing that mechanical ventilation aggravates existing lung injury, or even by in and of itself induces lung injury (ventilator-associated lung injury – VALI) [1][2][3].

Mechanical ventilation with large breaths (tidal volumes - $V_T$) is a known risk factor for the development of acute lung injury during the course of MV, even if no lung injury is present when MV is initiated [4]. In Sweden, approximately 7300 patients are identified annually as suffering from acute respiratory failure requiring mechanical ventilation, almost 1300 of them with the most severe form: ARDS [5]. Decreasing ventilator-associated lung injury by using lower $V_T$ (6 ml/kg) reduces mortality from 40 to 31% in patients with ARDS [6], a (seemingly) simple therapeutic maneuver spares more than 100 lives per year, in Sweden alone. However remaining mortality is still high.

Mortality, however, is seldom due to frank hypoxemia. Death is most often due to multiple organ failure, as MV comes along with negative side effects on virtually all organ systems and functions that are connected to the lung via circulatory, humoral and neural pathways [7][8].

Although some doubts have been raised recently [9], spontaneous breathing lacks the above side effect or even mitigates lung injury [10], and has further advantages as well.

The spontaneous inspiratory efforts of the diaphragm help in recruiting the dorsal dependent lung areas that are prone to collapse, particularly in the supine position [11][12].

The active inspiration might help to prevent diaphragmatic inflammation and atrophy that prolongs weaning or even make it a failure [13][14][15][16].

There are differences in the distribution of ventilation and lung blood flow, as well as in regional aeration of the lung and patency of lung tissue during spontaneous breathing and mechanical ventilation [17][18].

Finally, the spontaneously breathing patient has more freedom to follow his or her own timing and ventilatory demand, thus allowing for less sedation [19], which in itself may be beneficial. Indeed, less sedation is associated with decreased length of ventilation and subsequent mortality in ventilator-treated patients [20].

SB allowed during ongoing MV in ventilatory modes, as bi-level positive airway pressure (BiPAP) or airway pressure release ventilation (APRV), has
been shown to improve oxygenation in mechanically ventilated patients [21][22][23][24]. The current explanation of this effect is that SB (or more specifically diaphragm activity) recruits collapsed lung regions by increasing transpulmonary pressure in the dependent (dorsal) lung regions [18][22][23].

All studies demonstrating benefits of SB allowed for SB “on top” of the relatively high PEEP levels that are used with BiPAP or APRV, and did not control for small V\textsubscript{T} [21][22][23][24]. When combined with ongoing MV, however, even small spontaneous breaths can forcefully augment the tidal volume, and vice-versa, when a mechanical breath coincides with the patient’s own breathing effort, it might result in large V\textsubscript{T} [25].

However, it is not known whether spontaneous breathing is capable to improve oxygenation when following its natural pattern, i.e. when taking place at zero end-expiratory pressure and at a V\textsubscript{T} limited to 6 ml/kg [26]. We did not know whether a low pressure-small tidal volume SB, close to the true natural pattern and without PEEP, would be able to recruit collapsed lung areas and improve oxygenation as seen in the mentioned BiPAP/APRV studies. Being convinced that the cardiopulmonary system that nature has evolved is perfectly suited to operate during SB, we assumed that SB would result in improved oxygenation, even without high pressure-high volume recruitment.

The hypothesis, thus, was that spontaneous breathing would improve oxygenation by redistributing pulmonary blood flow from collapsed to ventilated areas, and that this effect should be, more or less, independent of the cardiac output.

This thesis will explore the above hypothesis in a porcine lung collapse model, specially designed to help answering this question.

**Porcine lung collapse model**

Common acute lung injury models induced by oleic acid or endotoxin show lung collapse but, in addition, inflammatory edema [27] and the lung lavage model (surfactant depletion) will usually cause severe hypoxemia at zero end-expiratory pressure, if not very carefully titrated [28].

Therefore we developed a porcine lung collapse model to produce standardized stable lung collapse with a shunt fraction that would be both high enough for the study of the related phenomena but not so high as to make SB unfeasible. Lung collapse was generated by negative pressure application (NPA): connecting -50 kPa of the central suction line to the endotracheal tube for 90-120 seconds. This technically very simple method results in stable lung collapse, plus hemodynamics and gas exchange, over a period of at least two hours making this model suitable for the study of lung collapse/recruitment phenomena.
As SB cannot be controlled as easily as mechanical ventilation, we chose to set mechanical ventilation (at least tidal volume and respiratory rate) according to the breathing pattern the animals adopted during SB. In earlier investigations, SB combined with ongoing MV was studied, and it is debatable whether those results reflect the effect of true SB or an SB modified by MV.

The breathing pattern the animals adopted was a rapid, shallow breathing, and the tidal volume of 6 ml/kg coincided with current recommendations for setting tidal volume during mechanical ventilation [6][26]. To the best of our knowledge, SB has never been studied with such a breathing pattern in this context before.

One-lung ventilation

To make sure that we are dealing with a non-recruitable lung collapse and, hence shunt, in Paper III we used one-lung ventilation (OLV). OLV is used in anesthesia to facilitate surgical access to intrathoracic structures, and in intensive care, when differential lung ventilation is necessary (e.g. due to bronchopleural fistula).

During OLV, one lung is isolated, either with a double lumen endotracheal tube [29] or bronchus blocker [30], while the other lung is ventilated. Receiving no ventilation, the non-ventilated lung collapses and major pulmonary shunt develops. This atelectasis, as the lung is isolated from ventilation, is not affected by airway pressure variations in the ventilated lung. When HPV is activated in the non-ventilated lung, blood flow is diverted towards the ventilated lung. This allowed us to study whether airway pressure in the ventilated lung affects the pulmonary shunt arising through the non-ventilated lung.

Ventilation/perfusion matching

The main function of the lungs is to provide adequate gas exchange that allows for the oxygenation of blood and the removal of the main waist product of the aerobic metabolism, carbon dioxide. A prerequisite for effective gas exchange is that alveolar ventilation (VA) and alveolar perfusion (Q) are matched. In alveoli where VA is disproportionately low compared with Q, the perfusing blood might not be fully oxygenated; an extreme example is atelectasis, when alveoli are collapsed without any ventilation. As the blood perfusing such alveoli is not saturated with oxygen, it might decrease the arterial partial pressure of O₂ (PaO₂). Conversely, in alveoli where VA is disproportionately high compared with Q, the excess ventilation cannot increase oxygenation and carbon dioxide removal; part of this ventilation becomes ineffective “dead-space” ventilation [31][32].
When lungs are healthy, perfusion is matched to ventilation approximately 1:1, and regulatory mechanisms of the lung try to preserve such a ratio even in diseased conditions. The main and most frequently studied regulating mechanism to maintain ventilation/perfusion (VA/Q) matching when VA decreases is the reflex of hypoxic pulmonary vasoconstriction [33].

Hypoxic pulmonary vasoconstriction

Hypoxic pulmonary vasoconstriction (HPV) is a pulmonary regulatory reflex described by von Euler and Liljestrand [34]. Pulmonary arteries constrict when the alveolar oxygen partial pressure (P\textsubscript{AO\textsubscript{2}}) is low, allowing for the redirection of pulmonary blood flow toward alveoli with higher O\textsubscript{2} content.

The essential sensor and effector responsible for HPV is the pulmonary arterial smooth muscle cell. As O\textsubscript{2} reaches those cells from two different sources (from alveolar gas and from mixed venous blood), the partial pressure of oxygen at the HPV sensor site (P\textsubscript{SO\textsubscript{2}}) is a weighted average of the P\textsubscript{AO\textsubscript{2}} and the partial pressure of oxygen in the mixed venous blood (P\textsubscript{vO\textsubscript{2}}). In the dog this is described by the equation: P\textsubscript{SO\textsubscript{2}} = P\textsubscript{AO\textsubscript{2}}^{0.62} + P\textsubscript{vO\textsubscript{2}}^{0.38} [35]. Although in the pig, lacking collateral ventilation, the above equation is probably slightly different [36], the principle stills holds true.

When alveolar gas is absent, such as in atelectasis, the partial pressure of O\textsubscript{2} at the HPV sensor site, and hence the main determinant of HPV activity, is P\textsubscript{vO\textsubscript{2}} [37]. HPV is affected not only by hypoxia, but by pulmonary artery and left atrial pressures, although the mechanisms are not clear [38].

From the onset of hypoxia, HPV reaches its maximum effect within 15 minutes, and is maintained at this level for several hours. The strength of HPV differs among species: pigs have strong HPV, humans have considerably weaker HPV [35].

Despite being considered weak in humans, HPV has important effects in maintaining arterial oxygenation in a variety of lung diseases [39]. Furthermore, a drug that potentiates HPV, almitrine, increases P\textsubscript{aO\textsubscript{2}} during one-lung ventilation [40] and in patients with ARDS [41].

Sodium nitroprusside

Sodium nitroprusside (SNP) is a nitric-oxide donor, and thereby a potent short-acting vasodilator relaxing vascular smooth muscle cells [42]. As the effector of HPV is the pulmonary arterial smooth muscle cell, SNP attenuates/blocks HPV [43][44].

SNP has a balanced effect on both the arterial and venous sides, and due to venous pooling, cardiac output usually remains unchanged during SNP
infusion, however when afterload markedly decreases due to arterial vasodi-latation cardiac output might increase [42].

SNP was used to block HPV activity in Paper IV, thereby allowing an assessment of to what extent HPV is involved in the findings discussed in this thesis.

Cardiac output dependency of the pulmonary shunt

The cardiac output (CO) dependency of pulmonary shunting during MV is a consistent phenomenon seen in different species [45][46] including humans [47], in healthy [48], as well as in focally [49] and diffusely [45] diseased lungs, and irrespective of whether CO is modulated pharmacologically [45][50], mechanically [45] or by bleeding / volume repletion [48].

The mechanisms responsible are, however, not fully elucidated. Increased blood flow, elevated $PvO_2$ [51][52], elevated mean pulmonary pressure and decreased pulmonary vascular resistance [45] all are associated with increased shunt. Sandoval et al proposes that $PvO_2$ mediates the CO dependence of pulmonary shunt [51]. This raises the possibility that HPV would act as the link between CO and pulmonary shunt, as HPV is attenuated not only by increased $PvO_2$, but by increased pulmonary artery pressure [38], as well.

Venous admixture

Based on mass preservation, venous admixture ($Q_{va}/Q_t$) is calculated from arterial, mixed-venous blood gas sampling and $Pao_2$, using a simplified two compartmental model of VA/Q matching. The two compartments in this model are fully oxygenated (arterial) and non-oxygenated (mixed-venous) blood [53][54]. $Q_{va}/Q_t$ indicates what proportion of mixed-venous blood should have passed alveoli without being oxygenated, to explain the oxygen content found in arterial blood [31][32].

Although it is widely used as a proxy for pulmonary shunt, $Q_{va}/Q_t$ is not equal to pulmonary shunt, as blood from non-collapsed alveoli with VA/Q less than normal (ventilation/perfusion inequality) also increases $Q_{va}/Q_t$ [31].

Multiple inert gas elimination

Multiple inert gas elimination (MIGET) is a technique allowing for detailed examination of the VA/Q matching. When six substances of different solubility (sulfur-hexafluoride, ethane, cyclopropane, enflurane, ether and acetone) are infused peripherally, steady-state sampling and calculation of the excretion and the retention of each substance enables the construction of a virtually continuous distribution of VA/Q ratios against blood flow or venti-
lation [55]. The standard deviation of the logarithmic distribution of perfusion ($\text{LogSD}_Q$) and ventilation ($\text{LogSD}_V$) can be calculated as measures of the dispersion (mismatch) of blood flow and ventilation, respectively. Shunt measured by MIGET is usually less than that calculated by $Q_{va}/Q_t$ [31].

**Computed tomography**

Computed tomography (CT) allows for constructing coronal slices using rotating x-ray. Based on their different radiological density, graded in Hounsfield unit (HU), various organs can be depicted and studied.

As densities for tissues (high) and gas (low) are markedly different, lungs can be examined by CT, and regions with varying gas/tissue contents can be differentiated [56]. As established earlier, over-aerated (-1000 – -850 HU), normally aerated (-500 – -850 HU), poorly aerated (-100 – -500 HU) and atelectasis (100 – -100 HU) can be differentiated [57]. Examinations can be transferred and regions of interest can be manually delineated then analyzed for volume and amount of lung tissue in different aeration categories by dedicated software [58].
The aims of this doctoral thesis

The main objective of the studies included in this thesis was to investigate whether spontaneous breathing at its natural pattern is per se capable of improving impaired oxygenation, and if so, by what mechanisms.

The specific aims of the studies were:

I. To evaluate whether spontaneous breathing improves oxygenation and lung aeration compared with mechanical ventilation at matched respiratory rate and tidal volume, and whether pulmonary blood flow and its redistribution differs between SB and MV.

II. To investigate whether our novel porcine lung collapse model, where lung collapse is induced by negative pressure application during muscle paralysis and mechanical ventilation, is hemodynamically stable over time; and how pulmonary shunt is affected by cardiac output during SB and MV.

III. To confirm that pulmonary shunt is independent of cardiac output during SB, as seen in Paper II, and to investigate whether airway pressure or hypoxic pulmonary vasoconstriction are involved in cardiac output dependency of the pulmonary shunt.

IV. To examine how inhibition of the hypoxic pulmonary vasoconstriction affects the beneficial effect of SB on pulmonary shunt seen in Papers I-II.

The knowledge obtained from the studies above might improve our understanding of the physiology of ventilation/perfusion matching in lungs, both in healthy and diseased conditions.
Material and methods

Animals

All experimental protocols were approved by Uppsala Animal Ethics Committee, and current Swedish regulations and legislations were followed in the design and conduct of experiments.

Fifty-two healthy, approximately 3-month old piglets of a Swedish country breed were used, purchased from purpose breeder. Animals had free access to food and water until being transported to the experimental facility, which was immediately preceded by IM premedication with 50 mg xylazin (Rompun® vet., Bayer Animal Health, Leverkusen, Germany).

Anesthesia

Identical anesthesia protocols were used in all studies.

After arrival at the experimental facility, the piglets were premedicated with IM tiletamine 2.2 mg·kg$^{-1}$ plus zolazepam 6 mg·kg$^{-1}$ (Zoletil®, Virbac, Carros, France). Following the placement of an 18G needle into an ear-vein, anesthesia was induced with ketamine 8 mg·kg$^{-1}$ and morphine 1 mg·kg$^{-1}$ IV, and maintained with IV infusion of ketamine 20 mg·kg$^{-1}$·h$^{-1}$ and morphine 1 mg·kg$^{-1}$·h$^{-1}$.

Following a 10 mL·kg$^{-1}$ IV bolus of dextran 60 (Macrodex, Pharmacia, Sweden), 10 mL·kg$^{-1}$·h$^{-1}$ Ringer acetate were administered intravenously throughout the experiment. Body temperature was closely monitored and kept constant by warmed fluids and heating pad.

At the end of the experiment animals were euthanized by an overdose of potassium IV while under deep anesthesia.

Instrumentation

In supine position, which was maintained during the whole experiment, a 9.0 mm ID endotracheal tube (Mallinckrodt, Athlone, Ireland) was inserted via a tracheotomy.

A central venous line and flow-directed pulmonary artery catheter (Criti-Cath SP5107H, Becton Dickinson, Singapore) were inserted via the right
external jugular vein. An arterial line was placed via a branch of the subclavian artery.

In Studies III and IV, for partial occlusion of the venous return an additional PA catheter was placed via a femoral vein cut-down, and floated cephaladly (usually just beyond 50 cm, approximately at the level of the diaphragm) until blood pressure dropped.

Cystostomy was performed for urine drainage, balloon catheters (Smart-Cath, Bicore Monitoring Systems, Irvine, CA, USA) were inserted in the distal esophagus for esophageal, and in the upper abdomen for intra-abdominal pressure measurement.

Ventilatory management

All animals were initially breathing spontaneously, connected to the ventilator (Servo 300 or Servo i, Maquet, Solna, Sweden), without positive end-expiratory pressure (PEEP) or pressure support (zero continuous positive airway pressure) with a triggering sensitivity of –1 cm H₂O and FiO₂ of 1.0 for 30 minutes. After preparation, the respiratory rate (RR) and tidal volumes (VT) were averaged over 2 minutes (= the control period) and were then used for setting RR and VT during the mechanical ventilation of the animal.

Three ventilatory modes were used in this thesis: spontaneous breathing (SB, Papers I-IV), mechanical ventilation (MV, Papers I-IV) and continuous positive airway pressure (CPAP, Paper III).

Spontaneous Breathing

If muscle relaxation was used, the ventilator was set to the same VT and RR the animal had adopted during the control period. When the effect of the muscle relaxant had worn off (if used at all), the ventilator was set to the zero CPAP mode with trigger sensitivity to -1 cmH₂O to achieve non-assisted spontaneous breathing with the animal connected to the ventilator.

Mechanical Ventilation

Volume-controlled ventilation was used in all studies. After muscle relaxation, VT and RR were set to the control period values, with zero end-expiratory pressure. Additional muscle relaxant was given intravenously once minimal deflections in the end-expiratory pause pressure indicated breathing activity.
Continuous Positive Airway Pressure

When the effect of the muscle relaxant had worn off (if used at all), the ventilator was set to the CPAP mode with trigger sensitivity of -1 cmH₂O, but no pressure support was applied. Mean airway pressure ($P_{aw}$) was set to correspond to mean $P_{aw}$ observed during MV.

Experimental protocols

Studies with lung collapse

The ventilator was set to the $V_T$ and the RR observed during SB, muscle relaxation (succinylcholine) was applied, and then lung collapse was generated by negative pressure application.

**Paper I**

Fifteen + 10 animals with induced lung collapse were randomized to SB and MV groups. The blood gas group of 15 animals was followed with blood gas analysis at 2.5 and 5 minutes and every 5 minutes up to 30 minutes, then every 15 minutes up to 90 minutes after NPA. In 8 of these animals (4 SB and 4 MV) ventilation/perfusion distribution was evaluated with MIGET by 45 minutes after NPA. In the CT group, arterial blood gas measurements and chest CT examinations were obtained at 2.5, 10, 20 and 30 minutes after NPA, according to a similar protocol as in the blood gas group but terminated at 35 minutes.

**Paper II**

Twelve animals with induced lung collapse were randomized to SB and MV groups. The animals were followed with blood gas analysis every 15 minutes until 135 minutes after NPA.

**Paper IV**

Eight animals were investigated during both SB and MV in a sequential manner with the start protocol being random. On completion of the measurements the other protocol was run (i.e.: SB was followed by MV and vice versa) after hemodynamics and oxygenation stabilized. Before running the second protocol (i.e. SB after MV and vice versa), a shorter NPA (30-60 seconds) was done to standardize atelectasis.

Within each protocol, following the stabilization of the $\text{PaO}_2/\text{FiO}_2$ after NPA (±10% difference between sequential measurements – usually 20-30 minutes), SNP infusion was started at 15 µg·kg⁻¹·min⁻¹ and titrated until the mean arterial pressure decreased by about 50%. Hemodynamic measurements were repeated and blood gases were taken 5 minutes after hemodynamics had stabilized on the SNP infusion.
Study with one-lung ventilation

**Paper III**

In 7 animals, a non-recruitable major shunt ($s_{maj}$) was induced by blocking the ventilation of the entire left lung with a 7 Fr spherical Arndt bronchial blocker [30] (Cook Medical Inc., Bloomington, IN, USA), which was placed and inflated in the left main bronchus under fiberoptic control. The minor shunt [59] ($s_{min}$) situation, induced by pure oxygen breathing during the preparation, always preceded $s_{maj}$; whereas within $s_{min}$ and $s_{maj}$ all particular settings (SB, MV, CPAP) were performed in random order, determined beforehand by internet randomizer (http://www.randomizer.org/form.htm).

**Measurements**

**Hemodynamics**

Heart rate from electrocardiography and arterial pressure were continuously sampled at 2000 Hz and recorded on a computer for off-line analysis (Bi-oPac Systems, Santa Barbara, CA, USA). Pulmonary arterial (systolic, mean and diastolic), pulmonary artery occlusion and central venous pressures were recorded on demand.

Cardiac output (CO) was measured by thermodilution technique (Solar 8000, Marquette, Milwaukee, WI, USA) using 3 injections of 10 ml ice-cold saline. The mean value is reported.

**Ventilation**

Respiratory flow signal was obtained by a Fleisch pneumotachograph (Series 3700, Hans Rudolph Inc., Shawnee, KS, USA) placed between the endotra-cheal tube and the Y-piece of the ventilator tubing, airway pressure ($P_{aw}$) was measured at the same location by pressure transducer (TSD104a, BioPac, Santa Barbara, CA, USA). Esophageal and gastric pressures were measured with similar transducers as $P_{aw}$, via balloon catheters inserted in the distal esophagus and in the upper abdomen, respectively. Respiratory parameters were continuously sampled at 2000 Hz and recorded on a computer for off-line analysis (BioPac Systems, Santa Barbara, CA). Respiratory rate and tidal volumes were obtained from the respiratory flow signal.

**Gas exchange**

At pre-specified time points, mixed-venous and arterial blood samples were drawn from the pulmonary artery and arterial catheters, respectively, for analysis (ABL3, Radiometer, Copenhagen, Denmark).
**PaO₂/FiO₂** was calculated as the ratio of the arterial partial pressure of oxygen to the fraction of inspired oxygen, set on and delivered by the ventilator.

Venous admixture, as a measure of pulmonary shunt, was calculated according to the Berggren equation [53]:

\[
Q_{va}/Q_t = \frac{(C_{CO₂} - C_{aO₂})}{(C_{CO₂} - C_{vO₂})};
\]

where \(C_{CO₂}\), \(C_{aO₂}\) and \(C_{vO₂}\) are pulmonary capillary, arterial and mixed-venous oxygen contents calculated from total hemoglobin saturation and physically dissolved \(O₂\) (from arterial and mixed-venous oxygen saturation and partial pressures).

**Multiple inert gas elimination**

Sulfur-hexafluoride, ethane, cyclopropane, enflurane, ether and acetone mixed in saline were infused in a peripheral vein. At steady state (usually after 30 mins) arterial and mixed venous blood samples were taken, tonometered with gas and analyzed together with an expired gas sample by gas chromatography (Model 5890, Series II; Hewlett-Packard, Walthem, MA, USA). Measures of the dispersion (mismatch) of blood flow and ventilation were calculated, as well.

**Computed tomography (CT)**

Helical chest CT scans were taken during inspiratory hold at 2.5 minutes and at 30 minutes after NPA in 10 animals (6 during SB, 4 during MV) with a similar, but truncated protocol as in the blood gas group. The end-inspiratory hold was used because it was the only option for obtaining images during an adequately long non-breathing period in the SB group. At end-expiratory hold the animals continued to breathe, whereas at end-inspiratory hold, probably due to the Hering-Breuer reflex, breathing activity ceased for a longer period [60]. Regions of interest were manually delineated and analyzed for volume and amount of lung tissue in different aeration categories by dedicated software (Maluna v2.04, University of Mannheim, Germany). Lung collapse was defined as densities from –100 to 100; poor aeration ranged from –500 to –100, normal aeration from –850 to –500 and over-aeration from –1000 to –850 HU.

**Plotting pulmonary perfusion pressure against cardiac output**

Pulmonary perfusion pressure was calculated (as \(P_{ppulm}=mPAP-PAOP\)) from mean pulmonary artery pressure (mPAP) and pulmonary artery occlusion pressure (PAOP). In order to assess the \(P_{ppulm}-CO\) relationship, as a measure of the pulmonary vascular tone [61][35], CO was decreased by graded balloon occlusion of the venous return in two steps. Hemodynamic measurements were taken at both steps when the mean arterial pressure had stabilized, and then \(P_{ppulm}\) was calculated and plotted against CO.
Statistical analysis

Power calculations were performed using known or assumed differences, standard deviations or coefficient of determination ($R^2$) to calculate group sizes needed at $\alpha = 0.05$ and at $1-\beta$ (power) = 0.8.

Values are presented throughout as mean [lower to upper 95% confidence interval, 95%CI]. Statistical significance was assumed when $p \leq 0.05$. All statistical analyses were performed with SPSS v20 (SPSS Inc., Chicago, IL, USA), or R environment for statistical computing (version 2.14 with lme4 package version 0.999375-42).

Studies I and II

Normally distributed variables were tested with t-test or two-way analysis of variance (repeated measures design, Student-Newman-Keuls post-hoc test), as appropriate. For some parameters, to avoid the statistical problems with repeated measurements, the area-under-curve was calculated assuming linear evolution between data points [62], and differences between groups were analyzed by the Mann-Whitney test. Associations were analyzed with linear regression or, in the case of serial measurements, as those measurements cannot be regarded as independent, with linear mixed-model regressions [63]. Variances were compared with an F-test.

Studies III and IV

Mixed-model analysis of variance was used for group comparisons, whereas the correlation between variables of interest was analyzed by linear mixed-model regression [63] on the raw data. For CO-adjustment of $Q_{va}/Q_t$ by mixed-model regression, CO was centered at its grand mean (3.6 L·min$^{-1}$) and intercepts were compared. Estimation of models and $R^2$ was likelihood-based [64] for hypothesis testing maximum likelihood, whereas for parameter estimates, restricted maximum likelihood estimation was used [65]. Backward stepwise multiple regressions and P values for fixed effects were calculated with a maximum likelihood test [65] (increase of -2*log-likelihood upon exclusion of the examined parameter). When multiple comparisons were made, P values were adjusted using the Holm procedure.
Results

**Paper I: Oxygenation during SB and MV**

With lung collapse, better oxygenation was seen in the SB group, compared with the MV group. SB exerted its beneficial effect on oxygenation within 30 minutes of the induction of lung collapse (Figure 1.).

Figure 1. PaO$_2$/FiO$_2$ during spontaneous breathing (open symbols) versus mechanical ventilation (solid symbols) in the blood gas (circles) and the CT part (rectangles) of the study. Symbols are mean values, error bars are 95% confidence intervals. #: SB value is significantly (P < 0.05) different from the corresponding MV value. *: significantly different from the first value (2.5 minutes) after lung collapse.

SB was associated with lower pulmonary shunt, as assessed by MIGET (Figure 2.). This finding was confirmed by subsequent studies with induced lung collapse (*Papers II and IV*) as well as one-lung ventilation (*Paper III*).
Figure 2. Alveolar ventilation (triangles) and pulmonary blood flow (diamonds) plotted against ventilation/perfusion ratios (VA/Q) by 45 minutes after lung collapse. Shunt (Qs/Qt; VA/Q=0) was higher during mechanical ventilation (solid symbols; MV) compared to spontaneous breathing (open symbols; SB). Symbols are mean values, error bars are 95% confidence interval.
#: SB value is significantly (P < 0.05) different from the corresponding MV value.

Paper I: Recruitment of collapsed lung during SB and MV

As studied by chest CTs, almost half of the lung tissue became atelectatic after NPA in both SB and MV groups (SB: 41.5% [35.4 to 47.6], MV: 45.9% [39.1 to 52.7]; P>0.05). With the breathing pattern adopted by these anesthetized animals, no obvious recruitment of collapsed lung areas took place in any group 30 minutes after NPA (SB: 39.1% [33.1 to 45.1], MV: 40.5% [36.3 to 44.7]; P>0.05). Despite the lack of any relevant recruitment, oxygenation improved in the SB group already at 30 minutes (Figure 1. rectangles).

Representative juxtadiaphragmatic CT slices taken at 2.5 and 30 minutes after lung collapse during mechanical ventilation (left panel) and spontaneous breathing (right panel) for individual animals. Numbers correspond to PaO2/FiO2 (mmHg) at the time of the CT scanning.
Paper II and III: Effects of cardiac output on the pulmonary shunt

The interpretation of Paper I was somewhat uncertain, as the SB group had lower CO than the MV group; and it is known that pulmonary shunt increases with increasing CO. In Paper II the CO was similar in groups; still SB resulted in better oxygenation.

It also indicated that, in contrast to MV, CO had no obvious effect on \( \frac{Q_{va}}{Q_t} \) during SB, i.e. shunt did not increase when CO increased. (Figure 3.)

Figure 3. Cardiac output (CO) and venous admixture (\( \frac{Q_{va}}{Q_t} \)) showed strong correlation in animals on mechanical ventilation (solid circles), but no such association could be seen in spontaneously breathing animals (open circles). The lines depict the regression equation, which was significant during mechanical ventilation only (solid line).

This latter finding was confirmed in Paper III, even when CO was intentionally modulated by partial occlusion of the venous return, both with minor shunt (healthy lungs) and with major shunt (one-lung ventilation). As assessed with decreasing CO, \( \frac{Q_{va}}{Q_t} \) correlated with CO during MV, but not during SB, at both levels of shunt. Interestingly, pulmonary shunt was CO-dependent even when \( P_{aw} \) was similar to MV in spontaneously breathing pigs (=CPAP) (Figures 4a,4b).

Figure 4a. Venous admixture (\( \frac{Q_{va}}{Q_t} \)) plotted against cardiac output (CO) during mechanical ventilation (panel A), continuous positive airway pressure (panel B) and unsupported spontaneous breathing (panel C) with minor pulmonary shunt (healthy lungs). The thick lines represents common regression, \( P<0.05 \) for the solid, \( P>0.05 \) for the hatched line.
Figure 4b. Venous admixture ($Q_{va}/Q_t$) plotted against cardiac output (CO) during mechanical ventilation (panel D), continuous positive airway pressure (panel E) and unsupported spontaneous breathing (panel F) with major pulmonary shunt (one-lung ventilation). The thick lines represent the fixed effect of CO, $P<0.05$ for the solid, $P>0.05$ for the hatched line.

**Paper IV: The role of hypoxic pulmonary vasoconstriction**

In Paper III, $Q_{va}/Q_t$ correlated with mixed-venous oxygen tension ($PvO_2$) during MV and CPAP, but not during SB. (Figure 5.)

Figure 5. Venous admixture ($Q_{va}/Q_t$) plotted against mixed-venous oxygen tension ($PvO_2$) during mechanical ventilation (rectangles – panels A, D), continuous positive airway pressure (diamonds – panels B, E) and unsupported spontaneous breathing (circles – panels C, F) with minor ($s_{min}$: open symbols – panels A-C) and major ($s_{maj}$: solid symbols – panels D-F) pulmonary shunt. Thick lines represent the fixed effect of $PvO_2$ (dotted line: non-significant regression).
When HPV was blocked by SNP, $Q_{va}/Q_t$ increased both during SB and MV. However SB still attained significantly lower $Q_{va}/Q_t$ than MV, even when CO-adjusted $Q_{va}/Q_t$ was calculated. (Figure 6.)

Figure 6. Venous admixture ($Q_{va}/Q_t$) during spontaneous breathing (SB - circles) and mechanical ventilation (MV- rectangles), without (empty symbols) and with sodium nitroprusside (+SNP – solid symbols) infusion. Large symbols indicate mean values, the bars are 95% confidence intervals.

Paper IV: Pulmonary vascular tonus during SB and MV

The slopes of the P$_{pulm}$-CO regressions were similar during MV and SB ($\sim$1.5 mmHg·min⁻¹·L⁻¹ [0.9 to 2.1]), indicating a similar hypoxic response when vasoconstriction was abolished by SNP during MV and SB. (Figure 7.)

The critical opening pressure of the pulmonary vascular bed (CO=0) was predicted to be 1.2 mmHg [-1.3 to 3.6] for SB, and 7.6 mmHg [3.4 to 11.8] for MV (P=0.0001 for the difference).

At the grand mean CO of 3.6 L·min⁻¹, the P$_{pulm}$ to perfuse lungs (and oxygenate blood) was found to be 6.7 mmHg [5.1 to 8.2] during SB and 12.6 mmHg [10.8 to 14.2] during MV. Mode of ventilation (SB vs. MV) and
mean $P_{aw}$ performed equally well in describing the variation of $P_{ppulm}$ with CO ($R^2=0.8$ for SB vs. MV+CO, $R^2=0.79$ for the $mP_{aw} + CO$ model).

Figure 7. Pulmonary perfusion pressure (mPAP-PAOP) plotted against cardiac output (CO) during sodium nitroprusside infusion under mechanical ventilation (solid symbols) and spontaneous breathing (empty symbols). The thin lines indicate the individual, whereas the thick lines indicate the common regressions. mPAP: mean pulmonary artery pressure, PAOP: pulmonary artery occlusion pressure.

Respiratory and hemodynamic stability in the models used

Both with lung collapse and one-lung ventilation, animals adopted a rapid, shallow breathing pattern ($V_T$ around 6 ml/kg, RR around 60/min). This pattern did not change after NPA (Papers I and II); however CPAP came with lower RR (Paper III).

The lung collapse model was reasonably stable both in terms of gas exchange and hemodynamics, as Paper II showed. One-lung ventilation did not affect hemodynamics, but oxygen consumption increased. (Paper III)
Discussion

Main findings

In the studies presented in this thesis, we found that:

- Gas exchange, shunt, cardiac output and hemodynamic performance are reasonably stable over time in this novel porcine lung collapse model. *(Paper II.)*

- Spontaneous small tidal volume / low pressure breathing without any support rapidly increases and achieves higher PaO₂/FiO₂ compared with mechanical ventilation at matched tidal volume and respiratory rate. *(Paper I.)*

- Improved aeration does not seem necessary in order for SB to improve oxygenation in partial lung collapse, as no major lung recruitment was seen on CT examinations despite improved oxygenation. *(Paper I.)*

- In contrast to mechanical ventilation, pulmonary shunt is not affected by cardiac output during unsupported spontaneous breathing, and seems to be independent of PvO₂. Pulmonary shunt becomes dependent on cardiac output and PvO₂ even during spontaneous breathing, when airway pressure is elevated. *(Paper III.)*

- Even when active vasoconstriction is blocked by SNP, pulmonary shunt is still lower during spontaneous breathing than during mechanical ventilation at matched ventilator settings. *(Paper VI.)*

Pulmonary shunt

SB attained lower pulmonary shunt and better oxygenation than MV at matched VT and RR with a similar amount of lung collapse in a porcine lung collapse model, as well as during one-lung ventilation. This finding calls into question the current explanation, that the principal mechanism responsible

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1 Both “true” pulmonary shunt (as determined by MIGET) and calculated venous admixture are henceforth jointly referred to as “pulmonary shunt”.

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for improved oxygenation during SB is recruitment of collapsed lung areas by diaphragmatic activity [18][66].

Previous experimental work [18][66][67] and human observations [24] use partial SB (in addition to ongoing MV) as BiPAP or APRV, when investigating the mechanism by which SB improves gas exchange. They conclude that SB “improves oxygenation mainly by recruitment of nonaerated lung and improved aeration of the lungs” [18]. It is also known that SB improves ventilation/perfusion matching [17][22]. However, it is interpreted as “redistribution of perfusion is possibly secondary to the altered ventilation” [66].

Recruitment of atelectatic lung tissue might require rather high pressure and volume [68], however normal tidal breathing is hardly able to create such pressure or volume. Recruitment is a possible mechanism in APRV or BiPAP in which the tidal volumes are not as small as the “biological” tidal volumes of natural SB adopted in our study, and relatively high PEEP levels are used, further increasing airway pressure.

Studying SB during small tidal volume / low pressure breathing without any support, pulmonary shunt was still lower in the lung collapse model, compared with MV at matched V_T and RR. As chest CT showed no sign of major recruitment, during either SB or MV, we concluded that “since aeration and ventilation patterns were unchanged the obvious alternative mechanism for an oxygenation improvement [i.e. reduction of pulmonary shunt] has to be a change in pulmonary perfusion pattern” (Paper I). This conclusion was further supported by the finding that SB attains lower pulmonary shunt even during one-lung ventilation, where the ventilated lung is recruited, and no further recruitment can take place (Paper III).

Cardiac output dependency of the pulmonary shunt

It was unexpected to find that CO and pulmonary shunt were unrelated when the animals were breathing spontaneously while, according to earlier findings in patients and animals, with MV a positive correlation exists [47][37][50].

The initial observation, based on the analysis of the spontaneous changes of CO on venous admixture (Paper II) was confirmed in a study where CO was intentionally modulated by partial occlusion of the venous return (Paper III). However, venous admixture was found to be CO-independent during SB only when airway pressures were low. With elevated airway pressure (CPAP), venous admixture was CO-dependent even when the piglets breathed spontaneously. Increased airway pressure is transferred along the airways towards alveoli augmenting the impedance of alveolar vessels [69]. With the impedance of those alveolar vessels of ventilated areas increased,
HPV might not be able to effectively divert pulmonary blood flow away from atelectatic lung areas.

PvO2 is proposed to mediate the CO-dependent pulmonary shunting [51], and this raises the possibility that HPV would act as the link between CO and shunt: PvO2 parallels CO (when oxygen consumption and oxygen affinity of hemoglobin are unaltered), and elevated CO is associated with elevated PvO2 which is known to attenuate HPV [37].

In Paper III, irrespective of the magnitude of the shunt, lower CO resulted in lower PvO2 (as VO2 was maintained), and, as expected [51][52], lower PvO2 was associated with lower Qva/Qt during MV and CPAP. However, despite an equally decreased PvO2, lower PvO2 was not associated with altered Qva/Qt during unsupported SB, where Qva/Qt was already lower than during MV. This finding challenges the concept that during unsupported SB the main mechanism of pulmonary blood flow redistribution is HPV, as in that case the HPV should have been less effective at higher PvO2 [37]. The PvO2-dependent HPV was either less important for the redistribution of pulmonary blood flow during SB (irrespective of the magnitude of the shunt), or a complementary, yet unidentified, mechanism redistributing pulmonary blood flow independent of HPV was active during SB.

Role of the hypoxic pulmonary vasoconstriction

HPV is considered to be the major reflex maintaining ventilation/perfusion matching. Although HPV is weaker in humans than in pigs, it is still considered clinically important in maintaining PaO2 within the context of both anesthesia and critical care [39][70].

The role of HPV in VA/Q matching during SB was, however, questioned by the finding that venous admixture, in contrast to MV and CPAP, did not correlate with PvO2 during SB in supine animals neither with minor shunt (healthy lungs) nor with major shunt (one-lung ventilation, Paper III). When HPV was blocked by SNP infusion in the porcine lung collapse model (Paper IV), venous admixture increased during SB. However, much lower venous admixture was still attained during SB, compared with MV. As venous admixture increased during blockade of HPV, it was concluded that HPV was active during SB. On the other hand, as venous admixture during SB with blocked HPV was approximately the same as venous admixture during MV with active HPV, one can speculate that a complementary, yet unidentified, mechanism helps redistributing pulmonary blood flow independent of HPV during SB. Based on the fact that venous admixture during SB with blocked HPV was approximately the same as venous admixture during MV with active HPV, it can be assumed that this mechanism is approximately as powerful as HPV is during MV.
To date, we are unable to identify this putative mechanism. We can only speculate that the negative intrapleural pressure generated during SB might have a role in pulmonary blood flow redistribution, as negative pressure ventilation has recently been shown to increase oxygenation and decrease pulmonary shunt compared to MV in surfactant depleted rabbits [71], as well as in patients with acute respiratory distress syndrome [72]. The observation that the effect of SB on pulmonary blood flow redistribution was lost during CPAP, where $Q_{\text{va}}/Q_t$ was found to be CO- and $PvO_2$-dependent, might support this hypothesis, as CPAP increases intrapleural pressure [73].

Model aspects

Both models used in these studies, porcine lung collapse and one-lung ventilation, were stable over a reasonable period of time and allowed for the comparison of SB and MV. In the lung collapse model, the pulmonary shunt and oxygenation stabilized within 30 minutes of the induction of lung collapse, and remained stable, just as hemodynamics and lung aeration, at least for two hours.

In both models, piglets adopted a rapid shallow breathing pattern that did not change either with induction of lung collapse, or with blocking the ventilation of the entire left lung. The tidal volume was $\leq 6 \text{ ml/kg}$, coinciding with the value advocated for protective ventilation of the lungs in patients [6]. As tidal volume and respiratory rate were matched to the tidal volume and respiratory rate at which those animals were breathing spontaneously, these models enabled us to compare the effects of the unsupported “real” SB with MV.

In the lung collapse model, thoracic CT showed approximately 40% of the lung tissue to be atelectatic. In contrast to previous work with APRV [18], no sign of major lung recruitment was found during SB in the lung collapse model, when studied with CT. The explanation we propose to these conflicting results is that in our lung collapse model tidal volume or pressure that was required to recruit collapsed lung [68] could not be built up, as SB in this setting was small tidal volume / low pressure breathing without any support.

Limitations

For visualizing lung collapse we had to take end-inspiratory rather than end-expiratory CT scans since the animals breathed vigorously during an end-expiratory pause. The effect of any tidal lung recruitment will be included in the end-inspiratory scans. However, earlier work has shown that the ventila-
tory phase has an insignificant effect on CT attenuation even at a $V_T$ of 10 ml/kg [74].

MV and SB were matched in terms of frequency and $V_T$, but this did not necessarily result in entirely identical patterns, since a breathing pattern is characterized by more than just volume and frequency. Non-monotonous breathing might have a favorable effect on oxygenation [75], and the biological variability – being effective in the SB animals – probably encompasses more than sighs [76].

In Papers II-IV, venous admixture was used as a measure of pulmonary shunt, and this is somewhat less accurate than the multiple inert gas elimination technique (MIGET). The venous admixture should roughly correspond with true shunt values [31] for two reasons: high FiO$_2$ (>0.6) was used and the absence of regions of low VA/Q ($0 < VA/Q \leq 0.1$) was also confirmed in the lung collapse model (Paper I) at similar FiO$_2$ as that reported by others in porcine OLV [77].

Ventilation/perfusion matching – an important issue of this thesis – heavily depends on HPV, and a number of factors could have influenced HPV in the porcine models. Although morphine [78] and benzodiazepines [79] (zolazepam) do not affect HPV, ketamine [80] (possibly even tiletamine, since it is also an NMDA-antagonist) and dextran [81] might have attenuated HPV somewhat. Respiratory acidosis, often seen in these experiments, theoretically also could affect HPV, although this still seems to be an unsettled issue. In isolated lungs hypercapnic acidosis improves HPV but only after 3 hours [82], a considerably longer time than our experiments lasted. In intact animals, hypercapnic acidosis increases pulmonary vascular resistance, without affecting the hypoxic response [83]; or attenuates HPV though complex mechanisms [84]. However in Papers III-IV, because (i) the animals served as their own controls, (ii) drug dosages were similar and unchanged over time, (iii) CO was similar in different ventilatory modes, and (iv) there were no significant differences in the arterial partial pressure of carbon dioxide among the ventilatory modes, it is unlikely that any of the factors listed above introduced bias into those studies. The results of Papers III-IV agreed with Papers I-II, although it must be recognized that individual variations might have influenced HPV and consequently the findings in those studies.

SB can promote alveolar recruitment [18], and affect ventilation distribution [85]. Because this was not explicitly studied, we cannot categorically exclude the possibility that regional ventilation, rather than regional perfusion was modulated by SB. This is, however, rather unlikely, as (i) in the lung collapse model with almost 40% of the lung tissue atelectatic no substantial recruitment of lung collapse was found within 30 minutes, neither during SB nor MV (Paper I) and (2) in both the lung collapse model (Paper I) and one-lung ventilation [77], MIGET shows the complete absence of low VA/Q (0<VA/Q<0.1) areas, whose improvement in regional ventilation could decrease pulmonary shunt.
We emphasize that our results and proposed explanations apply only to the particular range of CO and alveolar pressure observed in the studies, as very different scenarios are possible with a substantial increase of pulmonary blood flow in excess of the studied CO range [86].

Although our goal was to study unsupported SB, the piglets were connected to a ventilator even during SB. The reason was to be able to provide high FiO₂ accurately, in order to avoid hypoxia and facilitate calculation of PaO₂/FiO₂, as a measure of oxygenation. Even when no pressure support is set in the CPAP mode, the ventilator compensates for the pressure drop in the breathing circuit caused by the animals’ breathing effort during inspiration. It must be recognized that this compensation mounts a low level “hidden” pressure support of some centimeters of water. However, its importance in this context is not known.

As this porcine atelectasis model is novel, some caution must be exercised when interpreting and extrapolating the results obtained. However, similar SB-induced improvement in oxygenation and lower pulmonary shunt, without alveolar recruitment, has recently been found in the porcine lavage model, an established model of acute lung injury [87].

Finally, implications for the clinical contexts would be premature, when considering the differences in physiology between this porcine model and patients. Pigs have a stronger hypoxic pulmonary vasoconstriction (HPV) than humans [35], and this may exaggerate redistribution of blood flow compared with humans. Yet even in humans, a considerable effect has indeed been seen [88], and drugs that potentiate HPV (e.g. almitrine) has been successfully tested in patients with ARDS [41] or one-lung ventilation [40].

Acute lung injury and adult respiratory distress syndrome in the intensive care unit, or one-lung ventilation in the operating theater, consist of much more than just atelectasis. Caution should be exercised when extrapolating the above findings to patients.

Assembling the puzzle

The two distinct features of spontaneous breathing that were observed – namely decreased and CO-independent pulmonary shunt – could be considered as different aspects of the same phenomenon: SB improves ventilation/perfusion (VA/Q) matching. The alternative is that, if we look at the other side of the coin, MV induces VA/Q mismatch.

Hypoxic pulmonary vasoconstriction is accepted as the main factor of VA/Q matching. A prerequisite for HPV to work efficiently is for the pulmonary blood flow to be diverted away from collapsed areas whereby HPV has unopposed access to the non-collapsed lung areas. In isolated porcine lungs ventilated with FiO₂ 0.07 at zero end-expiratory pressure, the shift in
the pressure-flow curve in the pulmonary artery (a measure of HPV) is of the same magnitude as when lungs are inflated to 20 cmH₂O during normoxia [69]. One could possibly argue that improved VA/Q matching during SB could be explained solely by HPV being considerably more efficient during SB: as mean airway pressure is lower with SB than during MV, so is alveolar pressure, which could, concurrently, allow for lower resistance of alveolar vessels, thereby not impeding the redistribution of blood flow away from collapsed to ventilated lung areas, as MV does.

However, we present evidence that HPV might not be the sole or the major factor of pulmonary blood flow redistribution during SB, as with a blocked HPV, ventilation/perfusion matching was still better during SB. We can only speculate on that putative mechanism and think it might be the negative intrapleural pressure generated by SB that is responsible for the improved ventilation/perfusion matching seen during SB.

With all that in mind, we can reformulate the previous explanation for improved VA/Q matching during SB: the negative intrapleural (=low alveolar) pressure during SB, in contrast to the elevated intrapleural/alveolar pressure during MV, interferes less with VA/Q matching (which is at least partially independent of HPV). With an effective VA/Q matching in place increasing blood flow could be diverted toward ventilated lung regions by SB.

In Papers I and IV, the unopposed VA/Q matching during SB could more efficiently redistribute pulmonary blood flow toward aerated lung areas, even when HPV was blocked.

In Papers II and III, pulmonary shunt correlated tightly with CO during MV, as blood flow to collapsed lung areas increased with CO until the pressure built up was sufficient to overcome the resistance of vessels perfusing aerated lung areas, increased by the higher alveolar pressure. The low alveolar pressure, and unopposed VA/Q matching, of SB rendered the pulmonary shunt independent of CO.

Unfortunately, based on these experiments alone, we cannot assess the feasibility of SB with lung pathology such as ALI or ARDS. The decreased compliance, airway obstruction and concomitant metabolic changes in the rest of the body all pose increased load on the respiratory muscles [89], which can mount an inflammatory process [16] and induce dysfunction of those muscles [15], rendering – especially unsupported – SB almost impossible, but at least dangerous. Together with the fact that the ACURASYS study found mortality was improved by muscle relaxants given early in the course of ARDS [90], we would definitely not propose unsupported SB as a therapeutic modality in early severe ARDS.

However, one might consider SB not only as a therapeutic, but also as a diagnostic tool. Mortality increases with the days spent on a ventilator, so early liberation from mechanical ventilation is imperative [91]. A clinical deci-
sion must be made: does the patient cope with breathing on his/her own? To answer, one should be able to estimate the expected lung function and oxygenation when the patient is weaned from the ventilator.

Our results indicate that VA/Q matching is better during SB, which also means that MV itself interferes with VA/Q matching. Such interference might make the assessment of “oxygenation expected during SB” at least difficult, if not impossible. In contrast, assessment of oxygenation during an ongoing trial of unsupported SB might allow for a better assessment of oxygenation the patient is capable of on his/her own. Such information is of paramount importance when a decision about extubation is to be made e.g. as the patient emerges from general anesthesia after a major surgical procedure or when weaning the patient from mechanical ventilation.
Conclusions

Gas exchange, shunt, cardiac output and hemodynamic performance are reasonably stable over time in the novel porcine lung collapse model used in the studies presented in this thesis.

In the porcine lung collapse model, spontaneous small tidal volume / low pressure breathing without any support rapidly increased and achieved better oxygenation compared with mechanical ventilation at the same tidal volume and respiratory rate.

As the CT did not suggest any major lung recruitment, improved aeration does not seem essential for SB to improve oxygenation.

In contrast to mechanical ventilation, pulmonary shunt is not affected by cardiac output, and seems to be independent of PvO₂ during unsupported spontaneous breathing.

Pulmonary shunt becomes dependent on cardiac output and PvO₂ even during spontaneous breathing, when airway pressure is elevated.

Unsupported SB seems to improve ventilation/perfusion matching by a mechanism independent of or supplementary to the hypoxic pulmonary vasoconstriction.

Even when active vasoconstriction is blocked by SNP, pulmonary shunt is still lower during spontaneous breathing than during mechanical ventilation at matched ventilator settings. This latter finding indicates that SB might have similar beneficial effects on pulmonary shunt even in species with less strong HPV than piglets, such as humans.
Future perspectives

This work was done in animal models, and bearing in mind all the differences in physiology between porcine models and humans, these results might have limited implications, if any at all, for clinical practice at this stage. One of the most important differences among those mentioned above is the strength of HPV. However, given the fact that the beneficial effect of SB on VA/Q matching is at least partially independent of HPV, it might indicate that the same effect could be expected even in humans. If true this would certainly influence the way respiratory care is delivered.

One of the major indications of mechanical ventilation is severe VA/Q mismatch: hypoxia. It is a somewhat absurd situation that when a patient is severely hypoxic (i.e. has severe VA/Q mismatch), the therapy of choice is to institute mechanical ventilation, which itself impose (further) VA/Q mismatch. This controversy could be resolved if we could point out exactly what makes SB providing better VA/Q matching. That kind of knowledge would allow us to think about new modes of respiratory support, devoid of the adverse effects of the mechanical ventilation available today.
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References


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.