Regulation of Breathing under Different Pulmonary Conditions

BY

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Abstract

The breathing pattern of preterm infants is immature and is associated with a variety of reflexes. In a patient on the ventilator these reflexes interfere with spontaneous breathing. A better understanding of the immature control of breathing could lead to further improvements in ventilatory techniques. This thesis concerns studies of pulmonary stretch receptor (PSR) and phrenic nerve activity as part of the regulation of breathing in an animal model.

During assist/control ventilation with three different inspiratory pressure waveforms in animals with healthy lungs, squarewave pressure waveform strongly inhibits spontaneous inspiratory activity.

During partial liquid ventilation (PLV) in animals with healthy lungs, all PSRs studied maintained their phasic character, with increased impulse frequency during inspiration. PSR activity was not higher during PLV than during gas ventilation (GV), indicating that there was no extensive stretching of the lung during PLV.

During proportional assist ventilation (PAV) the applied airway pressure is servo-controlled proportionally to the ongoing breathing effort, thereby interacting with the activity of PSRs. Peak PSR activity was higher and occurred earlier during PAV than during CPAP. The regulation of breathing is maintained during PAV in surfactant-depleted animals before and early after surfactant instillation, with a higher ventilatory response and a lower breathing effort than during CPAP in both conditions.

Both lung mechanics and gas exchange influence the regulation of breathing. Inhibition of inspiratory activity occurred at a lower arterial pH and a higher PaCO₂, during PLV than during GV in animals with surfactant-depleted lungs, which might be related to recruitment of a larger number of pulmonary stretch receptors during PLV.

In summary, selected aspects of the regulation of breathing were studied in an animal model with different ventilatory techniques under different lung conditions similar to those that can occur in infants.

Keywords: Control of breathing, Pulmonary Stretch Receptor, Phrenic Nerve Activity, Respiratory Distress Syndrome, Surfactant, Partial Liquid Ventilation, Assisted Ventilation

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List of Papers

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


IV. Rieger-Fackeldey, E., Sindelar, R., Jonzon, A., Schulze, A., Sedin, G. Inhibition of breathing after Surfactant Depletion is Achieved at a Higher Arterial PCO₂ during Ventilation with Liquid than with Gas. (submitted)

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<tr>
<td>A/C</td>
<td>Assist-control ventilation</td>
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<tr>
<td>BHIIR</td>
<td>Hering-Breuer inspiratory inhibiting reflex</td>
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<td>CPAP</td>
<td>Continuous positive airway pressure</td>
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<td>ELBW</td>
<td>Extremely low birth weight</td>
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<tr>
<td>FiO₂</td>
<td>Fraction of inspired oxygen</td>
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<td>GV</td>
<td>Gas ventilation</td>
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<td>IMV</td>
<td>Intermittent mandatory ventilation</td>
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<td>PAV</td>
<td>Proportional assist ventilation</td>
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<td>Pₚᵢₚ</td>
<td>Airway pressure</td>
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<td>PEEP</td>
<td>Positive end-expiratory pressure</td>
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<td>PFC</td>
<td>Perfluorocarbon</td>
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<td>PIP</td>
<td>Peak inspiratory pressure</td>
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<td>PLV</td>
<td>Partial liquid ventilation</td>
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<td>PNA</td>
<td>Phrenic nerve activity</td>
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<td>Pₗᵼₑₛ</td>
<td>Oesophageal pressure</td>
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<td>PSR</td>
<td>Slowly adapting pulmonary stretch receptor</td>
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<tr>
<td>PSRᵢₚₚ</td>
<td>Instantaneous PSR impulse frequency</td>
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<tr>
<td>PTV</td>
<td>Patient-triggered ventilation</td>
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<td>RAR</td>
<td>Rapidly adapting pulmonary stretch receptor</td>
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<tr>
<td>RDS</td>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>RR</td>
<td>Respiratory rate</td>
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<tr>
<td>SIMV</td>
<td>Synchronised intermittent mandatory ventilation</td>
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<tr>
<td>Ti</td>
<td>Inspiratory time</td>
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<tr>
<td>Vᵢ</td>
<td>Tidal volume</td>
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Introduction

Survival of preterm infants has improved significantly since the 1990s as a result of advances in neonatal intensive care (1;2;3-4). This improvement has been attributed mainly to the use of antenatal corticosteroids (5;6;7), new ventilatory techniques (8;9) and surfactant treatment (10;11;12).

Patient-triggered ventilation (PTV) was introduced to avoid asynchrony of spontaneous breathing and ventilator-given breaths (13). During PTV mechanical breaths are triggered by the spontaneous inspiration. Assist-control and synchronised intermittent mandatory ventilation (SIMV) are the most frequently employed modes of PTV. Newer modes such as pressure support ventilation and proportional assist ventilation (PAV) have refined PTV. Further strategies have been investigated with the aim of avoiding lung injury induced by the ventilator (14). For example, ventilation with lower tidal volumes increases survival and reduces the number of days on the ventilator (15), inhaled nitric oxide improves gas exchange and decreases lung neutrophil accumulation (16), lung recruitment strategies such as high-frequency ventilation and partial liquid ventilation improve oxygenation (16).

The breathing of preterm infants is immature and is associated with a variety of reflexes, some of which are predominantly inhibitory in early life (17;18;19;20). The most well known of these reflexes is the Hering-Breuer inspiratory inhibiting reflex (BHIIR) (21), which terminates inspiration when a certain amount of volume or pressure has been reached. The varieties of reflexes interfere with spontaneous breathing efforts in a patient on the ventilator (22). A better understanding of the immature control of breathing could lead to further improvements in ventilatory techniques.

In the present project selected aspects of the regulation of breathing were studied in an animal model under different lung conditions and with different ventilatory techniques. All investigated lung conditions occur in preterm infants, such as the healthy lung, the surfactant-deficient lung and the surfactant-treated lung. The cat can be used as it exhibits a strong BHIIR similar to that in the human term and preterm infant (23).
Background

Regulation of Breathing

The Respiratory Centre

The breathing pattern originates in the lower parts of the central nervous system, the medulla and the pons (24). If the brain above the medulla is removed, breathing remains remarkably unchanged. All breathing efforts are terminated, however, if the connection between the spinal cord and the medulla is cut. Groups of neurons have been identified in the medulla: the dorsal respiratory group and the ventral respiratory group. The neurons of the dorsal respiratory group discharge spontaneously and are exclusively inspiratory, whereas the ventral respiratory group consists of both in- and expiratory neurons (25). The Pre Botzinger Complex located in the ventrolateral medulla plays a role in rhythm generation (26). The pontine respiratory group is situated around the medial parabrachial nucleus. It seems to be responsible for mediating rapid shallow breathing.

A circuit of neurons forms the ‘central pattern generator’, which starts a rhythmical process and produces a basic breathing pattern (27). Several models have been introduced in attempts to explain the neural mechanisms that initiate a respiratory rhythm (28). One way of explaining breathing is that inspiratory and expiratory neurons inhibit each other so that only one group will be active at the same time (29). According to another model inspiratory drive builds up until information concerning lung volume signals that an off-switch is warranted. This switches the system to expiration and the whole system is reset (30;31).

The basic breathing pattern formed by the central pattern generator is influenced by a variety of central and peripheral inputs, which are situated either in the brain, such as the central chemoreceptors, in other parts of the body, e.g. the peripheral chemoreceptors, or in the lung, such as the slowly adapting pulmonary stretch receptors (PSRs), the rapidly adapting pulmonary stretch receptors (RARs) and the C-fibre receptors (32). In addition, in mammals suprapontine regions exert a strong modulatory effect upon the basic respiratory drive generated in the brainstem (33). The origin of volun-
tary control is probably the motor cortex (34), and this affects breathing during exercise, hyperthermia and emotion. Some examples of voluntary control are breathing while singing, blowing, whistling, and playing an instrument. The voluntary pathways bypass the respiratory centre and fuel their information into the pyramidal tracts.

Central and Peripheral Chemoreceptors

The influence of central chemoreceptors is a prerequisite for adjustment of rhythmical breathing to ventilatory demands. Elimination of central chemosensitivity through cold block of a specific area on the ventral medullary surface leads to a marked reduction in respiratory activity and apnoea (35). Central chemoreceptors respond slowly to changes in pH and pCO₂ in the cerebrospinal fluid (36). Unlike peripheral chemoreceptors they are not stimulated by hypoxia, but are most sensitive to excess CO₂ (37). The carbon dioxide of the cerebrospinal fluid reacts with water and produces H⁺, which is the main stimulus of the central chemoreceptors. Long-term disturbances, for example in chronic lung disease, therefore modify the breathing rhythm significantly.

Peripheral chemoreceptors are most sensitive to lack of oxygen (38). These receptors consist of the carotid bodies, which mainly respond to PaO₂, and of the aortic bodies, which respond to reductions in PaO₂. Peripheral chemoreceptors respond within seconds and primarily increase the rate and/or volume of breathing. Stimulation of peripheral chemoreceptors from the carotid and aortic body can terminate apnoea and produce rhythmic ventilation if sufficiently stimulated (39).

Chemical control of breathing determines minute ventilation, with changes taking place over a matter of one or more minutes.

Pulmonary Receptors

Pulmonary vagal afferents contribute to modulating the respiratory rhythm and are mainly responsible for the respiratory pattern. They respond to inflation and deflation of the lung and to chemical agents. Impulses from these receptors are transmitted by the vagal nerve, in myelinated or unmyelinated fibres, to the central nervous system (40). Activity in myelinated fibres originates from PSRs or from RARs, whereas information in unmyelinated fibres originates from C fibres, sometimes named J receptors.

Slowly Adapting Pulmonary Stretch Receptors

PSRs are located within the smooth muscle layer of the airway (41;42), are more numerous than RARs and are easily identifiable (40). Their morphology has recently been demonstrated (43). PSRs continuously sense the tension within the myoelastic components of the airways (42) and respond to
stretching of lung tissue mediated by changes in lung volume, compliance, transpulmonary pressure (44), resistance (45) and airflow (46). PSR activity was first recorded by Adrian in 1933 (47). PSRs are classified as high-threshold PSRs if they discharge during inspiration and only rarely during expiration, and low-threshold PSRs if they discharge during both in- and expiration (48;49). PSRs can activate the BHIIR (21). The reflex response to lung inflation is termination of inspiration and the start of expiration. When the lung of an anaesthetised animal is kept inflated, it ceases to make inspiratory efforts for some time. It is thought that when a certain threshold of lung inflation is reached, inspiration is switched off and expiration begins (30).

![Pulmonary Stretch Receptor Activity](image)

**Figure 1.** Examples of the discharge of a high threshold (upper panel) and a low threshold (lower panel) slowly adapting pulmonary stretch receptor recorded during pressure controlled gas ventilation in two representative cats.
The activity of PSRs is not essential in human adults, since in patients with a lung transplant breathing continues even if the vagi are cut. In animals and in preterm infants PSR activity, however, seems to play a more important role. The BHIIR is stronger in newborn infants than in human adults (50), and preterm infants have a stronger BHIIR than do term infants have at birth (51). This reflex plays an important role in establishing rhythmic breathing in newborn infants, and diminishes over the first year of life (50;52). The modification of the breathing pattern induced by PSRs makes this pattern more efficient in terms of energy required. PSRs perceive the mechanical properties of the lung. They are primarily mechanoreceptors, but are also sensitive to changes in PCO₂ (53).

Rapidly Adapting Pulmonary Stretch Receptors

RARs rapidly adapt their frequency of discharge to a constant stimulus; that is, the frequency quickly returns to normal (40). Because of the rapidly changing discharge of these receptors the pattern can become erratic when the stimulus is frequently changing. RARs have an irregular discharge pattern and react to the rate of change of lung volume at high air flow or at end inspiration (54). The activity of RARs is inversely related to lung compliance (55;56). Besides their role as mechanoreceptors, RARs can also behave like chemical receptors (54). They can be stimulated by vapours such as cigarette smoke or by inhalation of irritating gases, which gave them the name “irritant receptors”, and they seem to be involved in coughing. RARs are situated in the superficial layers of the airways, the respiratory epithelium, and respond to probing (touching with a probe). They concentrate mainly in the larger airways at points where the airways divide. RARs can produce two opposite breathing patterns: rapid shallow breathing, and deep slow augmented breaths taken periodically (57;58). They also have a role in the initiation of the first deep gasps of newborn infants.

C Fibres

C fibres outnumber myelinated fibres in the lung and are also called J receptors because they are situated close to the pulmonary capillaries (juxta-pulmonary). A clear role for C fibres in normal human breathing has not yet been found. The receptors are stimulated by lung oedema, histamine, bradykinin and prostaglandins (57;60). Exogenous chemicals can also stimulate C-fibre discharge. The reflex response is apnoea, followed by rapid shallow breathing, hypotension, bradycardia, laryngospasm, coughing, and relaxation of skeletal muscles (59;60).
Phrenic Nerve Activity

Phrenic motoneuron output represents central inspiratory activity (40) (61). An increase in tidal volume and flow rate during mechanical ventilation results in a reduction in the peak amplitude of the integrated phrenic signal and in shortening of the duration of the phrenic nerve signal (62;63), with absence of this response after vagotomy. These effects are largely due to an earlier onset of late motoneuronal activities (64). There is an intact feedback loop from pulmonary vagal afferents to the inspiratory neural output of the phrenic nerve via the respiratory centre (63).

Figure 2. Schematic drawing of the duration of PNA and the number of PNA impulses (modified from Norsted T: Inhibition and stimulation of inspiratory activity. Dissertation from the Faculty of Medicine, Uppsala University, 1988).

Lung Mechanics

An important property of the lung is the ease with which it can be expanded and emptied in breathing. The so-called elastic recoil pressure of the lung is proportional to its elastance and is determined by the sum of tensions in the lung tissue (65). In the healthy adult half of the elastic recoil is attributable to the properties of collagen and elastin, which are the main elastic components of the lung tissue, while the other half is dependent on the surface tension of the air – liquid interface of the alveoli, the so-called liquid lining. Lung compliance is the reciprocal of elastance and is conventionally used to express the elastance of the lung. Compliance is measured as the ratio of change in volume to change in pressure, or can be displayed as a pressure-volume loop (66). In the preterm infant lung disease has a detrimental effect on lung function and increases the work of breathing: in respi-
ratory distress syndrome (RDS) the lungs are stiffened so that compliance is reduced.

Energy is expended to propel the air along the airways, a phenomenon known as resistance. Resistance is determined by the friction between the layers of air and the endotracheal tube and/or the airway walls (67), and can be measured as the ratio of change in airflow to change in pressure. Resistance is increased when a tube is in place or airway obstruction occurs.

Both a decrease in compliance and an increase in resistance increase the work of breathing.

Gas Exchange

Oxygen and carbon dioxide are transported by passive diffusion from the alveoli into the blood and from the blood into the cells of lung tissue or vice versa (68). The driving force of this process is the partial pressure of the gas on each side of a membrane (Fick’s law of diffusion). The diffusion is determined by the solubility of a gas (67). During partial liquid ventilation (PLV) there is a change in diffusion compared to that during gas ventilation (GV) as a result of a change in the solubility and concentration of the gas in a perfluorocarbon (69). Diffusion problems can occur in disease by thickening of the membranes (fibrosis) or by a reduction of the surface area (respiratory distress syndrome).

Pulmonary Conditions

Preterm infants have an immature lung and often suffer from disorders of lung growth, lung development and control of breathing. Infants most susceptible to lung injury are typically those with an extremely low birth weight (ELBW), born between 24 and 28 weeks of gestation (70). The last stage of lung development, the alveolar stage, starts at approximately 36 weeks. Most preterm infants are born in their saccular (terminal sac) phase, which comprises the gestational period of 24 - 36 weeks to term. In this phase the growth of the pulmonary parenchyma, the thinning of the connective tissue between the air space, and the further maturation of the surfactant system take place. ELBW infants can still be born in the canalicular phase which lasts from the 17th to the 26th week of gestation (70;71). The airway branching pattern is completed in this phase and the prospective gas-exchange region starts to develop. Infants born at this stage are more prone to develop airway and vascular lesions resulting in bronchopulmonary dysplasia (72). Besides the specific morphometry, the immature surfactant system and regulation of breathing have to be taken into account in attempts to avoid volutrauma, oxidant injury and inflammation/infection.
Respiratory Distress Syndrome

RDS is the most common respiratory disorder in preterm infants. This syndrome presents at birth, or shortly thereafter, with grunting respiration, chest wall retractions, nasal flaring and increased work of breathing (73). Hypoxaemia and hypercarbia are often present in this disorder. The radiological findings include hypoinflation, superimposed air bronchogram, and in severely affected babies almost non-aerated lung fields. The pathophysiology of the disorder has been elucidated. Basic problems are the immature structure and the surfactant deficiency of the lung resulting in a tendency to collapse (73;74). The surfactant-deficient lung has an increased elastic recoil, a decreased lung compliance and a reduced functional residual capacity (74) which together will lead to a ventilation-perfusion mismatch. The association of RDS with surfactant deficiency was described 45 years ago (75).

The surfactant deficiency in infants with RDS has been simulated in animal models by repeated lung lavages with saline (76;77).

Surfactant Treatment

Surfactant is a complex mixture of 80% phospholipids, 10% protein and 10% neutral lipids, mainly cholesterol. It is secreted by type II cells of the alveolar epithelium (78). The surfactant proteins play important roles in surfactant homeostasis, surfactant function and host defence (79). A lack of surfactant proteins precludes tubular myelin formation (a lattice-like structure of surfactant proteins) and thus promotes alveolar instability and collapse. The first isolation of surfactant was achieved by King and Clements (80) and the first clinical trial of surfactant treatment was conducted by Fujiwara (12). Surfactant replacement for RDS in preterm infants is probably the most thoroughly evaluated therapy currently used in neonatal intensive care units (73;81). It is widely accepted that surfactant replacement improves oxygenation, decreases ventilatory requirements, diminishes air leaks and reduces infant mortality from RDS (82;83;84).

Ventilatory Techniques

Gas Ventilation

Pressure-Controlled Ventilation

During intermittent mandatory ventilation (IMV), pre-set pressure-limited mechanical breaths increase the airway pressure at the end of the endotracheal tube, thereby creating a pressure difference between the airway open-
ing and the alveoli. The tidal volume applied is dependent on the elastic and resistive properties of the lung and on the parameters set at the ventilator: respiratory frequency (RR), positive end-expiratory pressure (PEEP), peak inspiratory pressure (PIP) and inspiratory time (Ti) (66). In between the breaths applied by the ventilator the patient can breathe spontaneously.

**Patient-Triggered Ventilation**

To avoid adverse effects caused by asynchrony of spontaneous breathing and ventilator breaths (22), patient-triggered ventilation (PTV) has been devised (13). In PTV the mechanical breaths are triggered by the spontaneous inspiratory breathing. The most frequently applied modes are assist-control ventilation and SIMV. In SIMV the ventilator is triggered by a number of preselected breaths within a certain time frame, while in assist-control ventilation the ventilator is triggered by every breath. No clear advantage of PTV over IMV has been proven, but several studies have shown improved oxygenation (85), more consistent tidal volumes (86), decreased fluctuation in cerebral blood flow (87), and decreased work of breathing. Triggering is achieved by means of trigger sensors (13). Problems in sensing spontaneous breathing in preterm infants or problems with the triggering device (delay, humidity, inappropriate triggering) have hampered the application of these techniques (88).

**Proportional Assist Ventilation**

Patients supported by proportional assist ventilation adopt their inherent spontaneous breathing pattern, which varies with their respiratory drive (89). During PAV the applied airway pressure increases in proportion to the instantaneous tidal volume and inspiratory airflow generated by the patient (90). Only PEEP and FiO₂ are preset. The patient fully controls the timing and degree of lung inflation. The “free” expression of the inherent breathing pattern can be achieved by setting the elastic gain in such a way that the work of breathing is shifted from the respiratory muscles to the ventilator and by setting the resistive gain such that the tube resistance and further resistance of the airways are compensated for. Back-up ventilation needs to be automatically initiated during apnoeas. The patient has unrestricted control of all breathing variables under such circumstances.

**Continuous Positive Airway Pressure**

Continuous positive airway pressure (CPAP) was used in adults as early as in 1936 (91), and was applied to spontaneously breathing neonates with respiratory distress in 1971 (92). CPAP is a technique for maintaining the end-expiratory airway pressure at a level higher than atmospheric pressure. Its application increased survival and improved PaO₂. The effects of CPAP have been ascribed to an increased functional capacity caused by recruiting atelectatic lung areas (93,94), reducing the work of breathing (95), reducing
resistance and increasing compliance. An improved regularity of breathing with a reduced respiratory rate and a reduced rate of apnoeic episodes has also been reported.

Partial Liquid Ventilation

Partial liquid ventilation (PLV) with perfluorocarbon (PFC) is a method of ventilatory support that was introduced by Fuhrman in 1991 (96). It is a combination of liquid and gas ventilation in which PFC is administered to the trachea in a volume equivalent to the pulmonary functional residual capacity, and in which the ventilation is maintained with conventional gas ventilation of the liquid-filled lung (96). The improvement of gas exchange during PLV is mainly due to recruitment of collapsed alveoli (97), achieved by decreasing the alveolar surface tension mainly in dependent parts of the lung. This results in decreased ventilation-perfusion mismatch and increased compliance (98). The beneficial effects of PLV on gas exchange and lung mechanics have been explored in animal models of RDS and meconium aspiration syndrome (99;100) and confirmed in adults and newborn infants with respiratory distress syndrome (101). In animals with healthy lungs PLV has been investigated regarding liquid distribution, lung mechanics, evaporative loss and gas exchange (69;102;103).
Present Investigations

Aims

The aims of these investigations were to gain further knowledge of the regulation of breathing under different lung conditions that occur in preterm infants and with different ventilatory techniques that are used in preterm infants. Studies were performed in a cat model

- to examine the effects of squarewave, sinusoidal and linear inspiratory pressure waveforms during pressure-controlled A/C ventilation on the firing pattern of PSRs and PNA

- to determine whether pulmonary stretch receptor activity in mechanically ventilated young cats with healthy lungs is different during PLV from that during GV

- to elucidate the ventilatory response before and early after surfactant instillation in terms of PNA and the activity of PSRs during PAV and CPAP in surfactant-depleted young cats

- to study lung mechanics and gas exchange at inhibition of PNA during controlled gas ventilation (GV) and during PLV before and after lung lavage

Material and Methods

Subjects

Studies were performed on juvenile healthy cats, which arrived at least 10 days prior to the beginning of the study to allow them to get acclimatized. The cats were maintained on standard laboratory food and water ad libitum and were kept on a 12:12 h light to dark cycle. They weighed 2.3 ± 0.1 to 4.4 ± 0.4 kg and were 3 to 5 months old.
The experiments were performed at the Biomedical Center of Uppsala University and were approved by the Uppsala University Animal Research Ethics Board (No. C 130 / 98; C 217 / 94; C 224 / 0; C 130/97).

Animal Preparation

Cats were anaesthetised with chloroform and placed in the supine position. An endotracheal tube (inner diameter 4.0 mm) was inserted orally into the trachea and tightly secured. The endotracheal tube was then connected to an infant ventilator (Stephanie®, F. Stephan Biomedical Inc., Gackenbach, Germany) and the animal was placed on pressure-controlled mechanical ventilation during the surgical procedures.

The right femoral vein and artery were dissected and catheters were inserted into these vessels until their tips were placed in the thorax close to the heart. Anaesthesia was continued with 0.72% α-chloralose (Sigma-Aldrich Chemie GmbH, Steinheim, Germany) (50 mg/kg) and maintained at regular intervals via the venous line. A continuous infusion of 10% glucose (2/3) and 5% 0.6M sodium bicarbonate (1/3) was given at a rate of 6.4 mL/kg/h (7.15 mg/kg/min of glucose) through the venous catheter throughout the experiment. The arterial line was used for continuous monitoring of blood pressure and intermittent determination of blood gases (Acid-Base Laboratory ABL 505®, Radiometer Corp., Copenhagen, Denmark). The cat’s core body temperature, measured as deep rectal temperature, was maintained at 38°C by a heating blanket and an overhead radiant warmer.

A pretracheal midline incision was performed for preparation of the trachea, the oesophagus and/or the vagal nerves and the phrenic nerves. A tight ligature was tied around the trachea to prevent air leakage around the endotracheal tube. An 8 French catheter with an oesophageal balloon (40 x 7.5 mm; flat frequency response up to 5 Hz) was inserted into the distal part of the oesophagus and a ligature was gently tied around the oesophagus to avoid entry of air into the stomach.

Preparation of vagal afferents: Both vagal nerves were exposed and the connective sheath was removed. The right vagal nerve was placed on a platform, and a slip of it was cut for further dissection into filaments under a microscope, leaving the major part of the nerve intact. The filaments were split into fine nerve strands, which were placed on a platinum electrode until single unit activity from a slowly adapting stretch receptor could be recorded. The left vagal nerve was left intact. To isolate and to prevent drying of the vagal nerves, the electrodes and the dissected area were submerged in mineral oil.

Preparation of the phrenic nerve: The left phrenic nerve was exposed and the connective sheath was removed under microscopic guidance. The intact phrenic nerve was then placed on two platinum electrodes and submerged in mineral oil.
Study Design and Protocols

**PSR Activity and PNA during Different Inspiratory Pressure Waveforms (Study I)**

The cats were exposed to periods of A/C ventilation of at least three minutes’ duration using three different inspiratory pressure waveforms: squarewave, sinusoidal and linear rise. Data from five to ten consecutive inflations were recorded at the end of every period of ventilation with each of the inspiratory pressure waveforms. CPAP of 0.2 kPa of at least the same duration as the A/C ventilation was applied before and after each of the test settings to avoid carry-over effects. The inspiratory time during spontaneous breathing on CPAP was set as the mechanical inflation time during the triggered ventilation (A/C) in each individual cat. The preset controlled ventilator rate was set below the spontaneous breathing rate so as not to interfere with the spontaneous breathing effort. PIP was set low so that the delivered $V_t$ would not overdistend the lungs as confirmed by $V_s$ in the lower range of normal $V_s$ for cats (14.9 mL/kg in our material; normal values for the cat 15-30 mL/kg) with maintained normal PaO$_2$ and PaCO$_2$ levels. PEEP was set at 0.2 kPa. The airflow signal elicited by the start of spontaneous inspiration was used to trigger the ventilator. The highest trigger sensitivity that did not lead to autotriggering in the presence of flow artifacts was chosen. The PEEP, mechanical inflation time and PIP settings in each cat were kept constant throughout the protocol. The fraction of inspired oxygen was uniformly set at 0.21. Arterial blood gases were determined after every recorded ventilatory setting.

**PSR Activity during PLV (Study II)**

Before the recordings were started the cats were kept normoventilated using controlled mechanical ventilation, as verified by arterial blood gases in the normal range, i.e. PaCO$_2$ of 4.4 to 5.6 kPa and pH of 7.38 to 7.42. The cats were then submitted to periods of pressure-controlled mechanical ventilation of at least 4 minutes using a squarewave inspiratory pressure waveform. PIPs of 1.2, 1.8, 2.2 and 2.7 kPa, with a PEEP of 0.5 kPa, were applied, always in the same order. RR given by the ventilator was set at 20/min (normal rate in cats: 10 – 20/min), $T_i$ was set at 1 second, and FiO$_2$ was kept at 0.21. Data from 15 consecutive breaths were recorded at the end of each of these four ventilatory periods, followed by determination of arterial blood gases.

Thereafter a bolus of 30 mL/kg prewarmed (38°C) PFC (Perfluorodecaline®, F2 Chemicals Ltd, Preston, Lancashire, UK) was instilled into the endotracheal tube via an adapter with a side port within 10 minutes, while PIP was increased to 2.2 kPa and FiO$_2$ to 1.0. Sufficient filling was ascertained by disconnecting the animal from the ventilator at the end of the fill-
ing procedure and observing that a meniscus could be seen at the endotra-
cheal tube at end-expiration. If no meniscus could be observed prior to re-
cording, additional PFC was added. After a stabilisation period of 10 min-
utes, the cats were submitted to four ventilatory periods with the same venti-
latory patterns, PIP and PEEP as used previously during GV, but with FiO₂
of 1.0. The order of the different PIP levels was reversed in every other cat
when PLV was used. Recordings and determination of blood gases were
performed as previously described.

**PSR Activity and PNA during PAV and CPAP in Surfactant-Depleted
Cats (Study III)**

The cats were exposed to a 3-minute stabilisation period of CPAP or PAV
before and after lung lavage and after surfactant instillation. Stabilisation
occurred within the first 3-5 breaths during each setting. Data from 10 to 20
consecutive breaths were recorded at the end of the 3-minute stabilisation
period. In order to rule out carry-over effects of the different ventilatory
modes, CPAP was applied before and after PAV under the three conditions
studied (before and after lung lavage, and after surfactant instillation). The
same end-expiratory pressure was set during PAV as during CPAP (0.2 kPa
before lung lavage and 0.5 kPa both after lung lavage and after instillation of
surfactant). Resistive unloading was set to compensate for the endotracheal
tube resistance only (2.0 kPa/L/s), and elastic unloading was set to compen-
sate for 75 % of the elastic recoil of the respiratory system.

To achieve surfactant depletion similar to that in RDS, lung lavage was
performed 7-8 times in between periods of conventional ventilation, through
the endotracheal tube with saline (30 mL/kg) heated to +37.5°C. After 30
minutes of stabilisation on conventional ventilation (PIP 2.0 kPa, PEEP 0.5
kPa, FiO₂ 1.0, RR 20 breaths/min), the cats were allowed to breathe sponta-
neously on CPAP and PAV. Following a period of mechanical ventilation
thereafter, the cats received an instillation of porcine surfactant (Curosurf®
100 mg/kg) through the tube, and after 10 minutes of stabilisation on con-
ventional ventilation they were allowed to breathe spontaneously on CPAP
and PAV.

**PNA Inhibition after Surfactant Depletion during GV and PLV (Study
IV)**

The cats were treated with 0.3 kPa PEEP, in order to monitor and record
the spontaneous breathing activity of each cat. Pressure-controlled mecha-
nical ventilation with a sinusoidal inspiratory waveform was then initiated
with the following settings: RR 60/min; Ti 0.33 sec; PIP 0.8 to 1.0 kPa using
a PEEP of 0.5 kPa. PIP was adjusted so that the blood gas values were in a
normal range. The FiO₂ was kept at 0.21. The PIP was then gradually in-
creased until rhythmical PNA disappeared. Three breaths after inhibition of
PNA, data from 20 consecutive breaths were recorded and arterial blood gases were analysed.

Thereafter lung lavage was performed by filling the lungs with warmed saline solution (37.5°C, 30 mL/kg) through a funnel connected to the endotracheal tube. Very gentle chest compressions were performed to allow the saline to be well distributed, before it was removed by suctioning. This procedure was repeated 7 to 8 times and mechanical ventilation was provided in between the lavage procedures. After a 30-minute period of stabilisation on mechanical ventilation (PIP/PEEP 3.0/0.5 kPa, RR 60/min, Ti 0.33 sec, FiO₂ 1.0), ventilation was increased until PNA was inhibited. Airway pressures were then recorded and arterial blood gases and pH were measured again.

In the next step a bolus of 30 ml/kg prewarmed (38°C) PFC (Perfluorodecaline®, F2 Chemicals Ltd, Preston, Lancashire, UK) was instilled into the endotracheal tube via an adapter with a side port. Instillation of PFC into the lung was performed within 10 minutes during pressure-controlled ventilation (PIP/PEEP 3.2/0.5 kPa, RR 60/min, Ti 0.33, FiO₂ 1.0). Sufficient filling was ascertained by disconnecting the endotracheal tube from the ventilator circuit at the end of the filling procedure and observing to see that a meniscus was present in the endotracheal tube at end-expiration. If no meniscus could be observed prior to recording, additional PFC was instilled prior to recording. After a stabilisation period of 10 minutes, the cats were studied with the same protocol during PLV as during GV, but with an FiO₂ of 1.0 and a PIP adjusted to blood gases in the normal range.

Measurements / Techniques and Data Acquisition

Airflow was measured by a sensor placed between the endotracheal tube connector and the Y connector of the tubing circuit of the infant ventilator. This sensor is a pneumotachometer with the dynamic properties of an original Fleisch 00 pneumotachograph, but with less dead space (0.6 ml) and resistance (1.1 kPa/l/s at 5 l/min). Airflow was calibrated with a precision flowmeter (Timeter RT 200®, Timeter Instrument Corporation, Lancaster, PA, USA). P aw was measured at the adapter of the endotracheal tube. P oes was recorded from the oesophageal balloon catheter by a pressure transducer (Druck Ltd. Transducer, Leicestershire, UK). P zw and P oes were calibrated with a water manometer. Arterial blood pressure was measured and heart rate recorded using the same type of transducer (Druck Ltd. Transducer, Leicestershire, UK), connected to the arterial catheter with the tip of the catheter at the same level as the transducer. Continuous recordings of arterial blood pressure and heart rate were made with a polygraph recorder (Recorder 330P®, Hellige AG, Freiburg, Germany).

Nerve signals from PSRs were amplified, filtered and rectified with a Neurolog system® (Digitimer Research Instrumentation Inc., Welwyn Garden City, Hertfordshire, UK; preampifier NL 103, AC amplifier NL 105,
filters NL 115). With the use of an analogue window discriminator (Digitimer D 130, Welwyn Garden City, Hertfordshire, UK), only signals from a certain single fibre were recorded without background noise. The signals were displayed on an oscilloscope (Tektronix Inc., Portland, Oregon, USA).

PNA was amplified, filtered and rectified with the same system. The rectified nerve signal was fed to a spike trigger to produce spikes of uniform amplitude and subsequently integrated by a resistance-capacitance low-pass filter with a leak (time constant 250 ms), providing a moving time average of PNA. Monitoring of the signals was achieved by means of an oscilloscope.

Signals of air flow and $P_{aw}$ were obtained directly from the analogue outlets of the ventilator. Together with signals of $P_{oes}$ and PNA they were transferred to an analogue-digital converter and recorded on disk at a sampling rate of 10 kHz per channel by a data acquisition system (Windaq Pro+, Dataq Instruments Inc., Akron, OH, USA).

**Data Analysis and Statistics**

Windaq Playback® Software (Dataq Instruments, Inc., Akron, OH, USA) was used to review the recorded signals. Analyses were performed by Windaq Playback® and Excel® (Office 2000, Microsoft Corporation, USA).

**Ventilatory Parameters and Lung Mechanics:** The airflow signal was integrated to tidal volume. Lung compliance was calculated as the delivered tidal volume divided by the difference between PIP and PEEP (Study I).

Gas flow, positive $P_{aw}$ and $P_{oes}$ were measured at the different PIPs. The airflow signal was integrated to obtain $V_t$ at PIPs (Studies II and IV). Transpulmonary pressure was calculated as $P_{aw}$ minus $P_{oes}$. The dynamic lung compliance was calculated as $V_t$ divided by the transpulmonary pressure at end of inspiration, when no gas was flowing (Studies II, III and IV).

**Gas Exchange:** After all recorded settings a blood gas analysis was performed.

**Nerve Signals:** The following variables were evaluated: The response time, i.e. the length of time from the start of the phrenic nerve burst to the onset of the triggered mechanical inflation and the time from the onset of the triggered mechanical breath to the end of the phrenic nerve burst; the duration of PNA, which is the time from the onset to the end of the phrenic nerve burst; the amplitude of the integrated PNA, which is the total number of impulses in the phrenic nerve burst, and also the amplitude of PNA at the time of onset of the triggered inflation; (Studies I and III).

The amplitude of the integrated PNA was monitored and the inhibition of spontaneous breathing activity was defined as occurring at the total disappearance of PNA, i.e. at the total inhibition of inspiratory activity (Study IV).
The PSRs were classified as follows: High-threshold PSRs, if they discharged during inspiration and rarely during expiration, and low-threshold PSRs, if they continued to discharge during expiration (Studies I, II and III). The 15 breaths recorded in each ventilatory period were visualised, and as no obvious differences were found among them, the first three breathing cycles were evaluated. The total number of PSR impulses per ventilatory cycle was obtained by adding up all impulses during in- and expiration (Study II). The instantaneous impulse frequency of PSR activity (\( PSR f_{imp} \)) was calculated from the time interval between two consecutive spikes (impulses * s\(^{-1}\)). \( PSR f_{imp} \) at the start of inspiration was determined from the interval between the first two spikes at the beginning of inspiration as defined as the start of increase in flow. Peak \( PSR f_{imp} \) was determined from the shortest interpeak interval during inspiration. Time to peak burst frequency was defined as the time interval between the onset of each breath and the peak \( f_{imp} \) (Studies I, II and III).

**Statistics:** Data on five consecutive breaths were evaluated for each setting (Study I). The first three breathing cycles were evaluated (Study II). Ten to twenty breaths were assessed at the settings studied (Study III) and after inhibition of PNA (IV).

One-way repeated measure analysis of variance (RM ANOVA) was used, unless otherwise stated, to test for differences between different pulmonary conditions or techniques (Studies I, III and IV). Student-Newman-Keuls tests (Studies I and IV) or \( t \)-tests for paired observations (Study III) were applied to evaluate differences. Data are given as means and standard deviations. Paired two-tailed \( t \)-tests were applied for comparison of data between GV and PLV (Study II). Pearson’s correlation coefficient was used to describe the linear correlation (\( r \)) between \( PSR f_{imp} \) and transpulmonary pressure (Study II). \( P \) values <0.05 were considered significant.

**Results**

**Effects of the Inspiratory Pressure Waveform During Patient-Triggered Ventilation on PSR Activity and PNA (Study I)**

Mean PSR activity was higher with the squarewave pressure waveform than with the other two pressure waveforms (\( p < 0.05 \)), although peak PSR activity was the same with all three pressure waveforms. The increased mean PSR activity during ventilation with the squarewave pressure waveform was accompanied by a longer duration of sustained end-inspiratory tidal volume. Significant differences were observed between the three pressure waveforms in the duration of sustained end-inspiratory tidal volume: 0.55 ± 0.17 s with
the squarewave pressure waveform, 0.24 ± 0.14 s with the sinusoidal pressure waveform and 0.14 ± 0.09 s with the linear pressure waveform (mean values for all cats; p < 0.01). This result was paralleled either by a prolonged peak PSR activity during the mechanical inflation or by sustained PSR activity during the early phase of expiration.

The duration of the PNA burst was shorter and the total number of impulses in the PNA burst was smaller during the squarewave pressure waveform than with the other ventilatory modes, including CPAP (p < 0.05).

During the inflation with the three different waveforms there were no changes in arterial PaCO₂ and pH.

PSR Activity during PLV in Cats with Healthy Lungs (Study II)

All PSRs recorded in the 10 cats maintained a similar phasic character with an increased impulse frequency during inspiration both during PLV and GV, with some differences in impulse distribution. PSR f_{imp} at the start of inspiration was lower at PIP 1.2 kPa and higher at PIP 2.7 kPa during PLV than during GV (p < 0.05). Peak PSR f_{imp} was lower at PIP 1.2 kPa (p < 0.05) and somewhat lower at PIP 2.7 kPa (p = 0.10) during PLV than during GV, resulting in a smaller number of PSR impulses at these two settings during PLV than during GV (p < 0.05).

Only when a low PIP of 1.2 kPa was applied was V_t significantly higher during GV than during PLV (p < 0.01). Dynamic lung compliance was lower during PLV than during GV both at a PIP of 1.2 kPa (p < 0.01) and 1.8 kPa (p < 0.05). Pearson’s correlation coefficient between PSR f_{imp} and transpulmonary pressure ranged from 0.6 to 0.8 (mean values) during both GV and PLV and did not differ between these two conditions. Blood gases were in the normal range at a PIP of 1.2 kPa (Table 1). When PIPs of 1.8, 2.2 and 2.7 kPa were applied, all cats were hyperventilated during GV and PLV. Blood gases differed between GV and PLV at a PIP of 1.2 kPa. When peak PSR f_{imp} values obtained from measurements during GV and PLV were related to their V_t values, a curvilinear relationship was observed at PIPs of 1.2 - 2.2 kPa.

PNA and PSR Activity during PAV and CPAP in Surfactant-Depleted Cats (Study III)

V_t and RR were higher, with lower PaCO₂ and higher PaO₂, during PAV than during CPAP both before and after surfactant instillation (p<0.05; both conditions).

After lung lavage, arterial PaCO₂ was lower during PAV than during CPAP, which was explained by an 84% higher V_t and an 18% higher RR during PAV than during CPAP. After instillation of surfactant, arterial pH,
Vt and RR remained higher and PaCO₂ lower during PAV than during CPAP.

Before lung lavage there was no difference in PNA between PAV and CPAP. As an indicator of breathing effort, both the ΔPoes and the PNA were lower during PAV than during CPAP in both conditions after lung lavage (p<0.02). After lavage the decrease in PNA amplitude and duration during PAV, concomitantly with the decrease in Poes and the increase in Vt, was immediate when CPAP was switched to PAV.

Before lung lavage, there was no difference in peak PSR f_imp between PAV and CPAP. After lung lavage the peak PSR activity was higher and occurred earlier during PAV than during CPAP (p<0.01), and correlated linearly with PNA duration in all conditions studied (p<0.001).

Inhibition of Breathing after Surfactant Depletion is Achieved at a Higher Arterial PCO₂ during Ventilation with Liquid than with Gas (Study IV)

Inhibition of PNA occurred at a lower PIP, a lower transpulmonary pressure and a lower Vt before lavage than after lavage. Compliance at inhibition of inspiratory activity was higher before than after. Resistance was lower before than after lavage during GV.

After lavage, PIP and transpulmonary pressure were similar at inhibition of PNA during GV and during PLV. After lavage, compliance at inhibition remained the same during both modes of ventilation and resistance was lower during GV than during PLV.

Before lavage, during GV inhibition of PNA occurred at an arterial pH of 7.42, which did not differ significantly from the post lavage arterial pH at inhibition of PNA. There was no statistically significant difference in arterial pH at PNA inhibition between GV and PLV. At inhibition of PNA the arterial PCO₂ was lower during GV before lavage than after lavage, and it was higher during PLV than during GV after lavage. Arterial PO₂ was at a level which provided sufficient oxygenation at all settings.

Discussion

Preterm newborn infants have an immature regulation of breathing, which is influenced by a number of reflexes. The spontaneous breathing efforts are influenced by these reflexes when the infant needs mechanical ventilation, and in that situation the reflexes may give rise to breathing that is not synchronous with the insufflations given by the ventilator. In addition, in preterm infants the regulation of breathing may differ depending on the lung
condition. A better understanding of the immature control of breathing could lead to further improvements in ventilatory techniques.

We showed in study I that in a cat model, different inspiratory pressure waveforms during A/C ventilation (85;104;105) had different inhibitory effects on spontaneous inspiratory activity as recorded from the phrenic nerve. A squarewave pressure waveform caused more marked inhibition of the spontaneous inspiratory activity than a sinusoidal or a linear pressure waveform. This inhibition can be explained by earlier peak PSR activity during inspiration and prolonged PSR activity during expiration. The inspiratory pressure waveforms differed regarding the time taken to reach PIPs. PIP was reached more quickly with the squarewave pressure waveform than with the linear and sinusoidal pressure waveforms. Although the different pressure waveforms did not result in different Vts or different response- and mechanical inflation times, the PIP was sustained for a longer period of time with the squarewave pressure waveform than with the other pressure waveforms. This bears some resemblance to the end-inspiratory occlusion technique for eliciting the inhibitory effect of the BHIIR (106) on spontaneous breathing, as observed in the present study in the markedly lower phrenic nerve activity during A/C ventilation with the squarewave pressure waveform than with the other pressure waveforms. Clark and von Euler proposed that a certain volume must be inflated in order to elicit the termination of inspiration, and that a larger volume delivered during the same time span is required to shorten the duration of inspiration (107). In our first study we found a highly linear relationship between the duration of the PNA and the tidal volume with all pressure waveforms when the mechanical inflation occurred late in inspiration (> 35%).

Our findings show that the inspiratory pressure waveform chosen influences the spontaneous breathing effort during pressure-controlled A/C ventilation and may indicate an earlier switch from inspiration to expiration during the squarewave pressure waveform.

In study II we demonstrated that PSR activity was not higher during PLV (100;108) than during GV in cats with healthy lungs. PLV with perfluorocarbon is a method of ventilatory support introduced by Fuhrman in 1991, wherein gas is ventilated into a partially liquid (perfluorocarbon) filled lung (96). PLV has been shown to decrease the alveolar surface tension mainly in dependent parts of the lung, resulting in alveolar recruitment and reduced ventilation-perfusion mismatch, and thereby improving gas exchange and lung mechanics (109). These beneficial effects of PLV have been demonstrated not only in animal models of respiratory distress and meconium aspiration syndrome (99;100), but also in adults and newborn infants with severe respiratory distress syndrome (101;110).

The PFC we used evaporates very slowly because of its low vapour pressure, but the high viscosity of Perfluorodecaline® might influence its distribution in the lung and increase the work of breathing (111). Theoretically the
high density of PFC and the altered surface tension of a liquid-filled lung might result in overdistension of the alveoli, leading to a higher discharge by the mechanoreceptors in the distal airways. Our findings do not support this concept, since the PSR discharge during PLV was either equal to the discharge during GV or even lower. During PLV all receptors maintained an impulse pattern with a phasic character similar to that during GV. Filling the lung with PFC might possibly increase the functional residual capacity and influence the PSR discharge pattern during expiration, especially that from low-threshold receptors located in the distal airways. In this study, however, all high-threshold receptors maintained their low burst activity during expiration and the single low-threshold receptor discharged continuously during expiration with both PLV and GV. The activity of one slowly adapting PSR was studied in each animal without knowledge of the location of the receptor in the lung and without any information on the activity of other receptors that may have contributed to the afferent information to the respiratory centre. Even if the distribution of gas or liquid in the lung might possibly vary between individuals, the recorded PSR activity was quite similar in all animals studied. The smaller number of PSR impulses, the lower PSR activity at the start of inspiration and the lower peak PSR activity at a PIP of 1.2 kPa during PLV compared to that during GV might be related to the fact that at a low PIP a viscous and heavy PFC will not easily be displaced into the distal segments of the lung. At a PIP of 2.7 kPa the higher PSR activity at the start of inspiration and the lower peak PSR activity during PLV than during GV may indicate that PFC remained inside the distal airways during the rapid changes in volume and pressure occurring in the breathing cycle. Besides being influenced by volume and pressure (45;44), the activity of the receptors may be affected by the flow rate (46), which might be lower during PLV and cause smaller tidal movements than with GV. At the highest PIP used the higher PSR activity at the start of inspiration during PLV compared to that during GV might indicate more marked stretching of the lung tissue at the beginning of inspiration, probably as a consequence of the inertia of perfluorocarbon. On the other hand the lower peak PSR activity during PLV compared to that during GV might imply less stretching at the highest ventilatory pressure. This could mean that there is less mechanical stretching at very high pressures with partial liquid ventilation than with gas ventilation. Thus PLV might reduce lung damage when very high airway pressures are applied.

We showed that there is no indication of excessive stretching of the lung with PLV, which might be important to know if PLV is to be applied in newborn infants, especially in those born preterm.

In study III we found that cats maintained their control of breathing during PAV both after lung lavage and early after instillation of surfactant, with a higher V, and RR at a lower PNA and ΔPoes compared to the results during CPAP. The time course of and changes in PSR fimp are in concordance with
the changes in the duration of PNA, indicating that PSR activity is involved in the control of breathing during PAV. In a succession of experiments, PAV has been investigated in a variety of animal models, with or without lung injury (89;112;113), and also in infants with mild RDS (90). The present studies showed improved ventilation and oxygenation during PAV in comparison to spontaneous breathing on CPAP, and maintained gas exchange with a lower transpulmonary pressure than with A/C ventilation and IMV. The breathing during CPAP remained rapid and shallow after instillation of surfactant. RR and Vt were both higher during PAV than during CPAP, resulting in a persistently higher minute volume. Rapid and shallow breathing with slightly increased lung compliance after instillation of surfactant has been described by other authors (114;115), and has been explained by Jobe (116) as an upward shift in the pressure-volume slope as a result of an increased functional residual capacity. In the present study, the difference in breathing pattern between PAV and CPAP was most clearly observed after lung lavage, with a shorter Ti during PAV than during CPAP, leading to a lower I:E ratio. This could be explained by an earlier and more rapid increase in inspiratory air flow during PAV, whereby the maximal Vt was reached earlier. In fact, with other techniques for insufflation, Clark and von Euler (107) observed in human and animal studies that when a gain in inspiratory air flow was superimposed on spontaneous breathing, the duration of inspiration was shorter. They ascribed this observation to the volume information supplied by vagal afferents to the respiratory centre, as the inverse relationship between Vt and Ti disappeared in vagotomised cats. The most striking effect of PAV on PNA both after lung lavage and after surfactant instillation was a markedly shorter duration of PNA during PAV than during CPAP, illustrating a lower inspiratory effort and reduced work of breathing during elastic unloading. Pack et al (117) described the characteristics of PNA during different ramp inflations in cats with normal lungs, and showed that the immediate increase in PNA with increased air flow was abolished after vagotomy, suggesting that PNA is modified by afferent vagal activity. In the present study, there were no differences in Vt, PNA (duration and amplitude) or PSR $f_{imp}$ between CPAP and PAV in cats with normal lungs. After lung lavage a higher Vt and RR, and a higher PSR $f_{imp}$ and transpulmonary pressure, concomitantly with a lower PNA, were observed during PAV in comparison with those during CPAP, indicating influence of PSR activity on PNA. It can be concluded that in surfactant-depleted cats, the regulation of breathing is maintained both before and early after surfactant treatment during CPAP and PAV, but with an increased depth and a higher rate of breathing and a lower breathing effort during PAV than during CPAP. The highly linear correlation between the PSR activity and duration of PNA indicates the importance of PSRs in the regulation of breathing during PAV under these conditions.
Study IV showed that in cats ventilated with gas, inspiratory activity is inhibited at higher peak airway pressures and tidal volumes after lung lavage than before. In cats with surfactant-depleted lungs, inhibition of inspiratory activity occurs at about the same airway pressures and tidal volumes during GV and during PLV (96;97;100), but at higher arterial PCO$_2$ during PLV than during GV.

In study IV a ventilatory strategy with PEEP (0.5 kPa) and positive pressure ventilation at 60/min was chosen in a model of surfactant depletion to simulate a relevant clinical situation in which lung recruitment and possible low tidal ventilation could be promoted. Lung compliance did not differ between PLV and GV in surfactant-depleted lungs, but resistance was higher during PLV, as reported elsewhere (97). This might not represent a real increase in resistance of the airways, but is more likely due to higher inertia of the liquid than of the gas. After lavage, the mean values for arterial PaO$_2$ were always adequate and higher during PLV than during GV at an FiO$_2$ of 1.0, as observed in other studies on PLV both in paralysed and spontaneously breathing surfactant-depleted animals (97;118;119). In animals with surfactant-depleted lungs, which may be partially atelectatic, mechanoreceptors in some well-ventilated areas may be active, whereas other receptors in atelectatic areas may be silent. In this study inhibition of PNA occurred at much higher airway pressures after than before lung lavage during GV, but at similar arterial blood gases before and after lavage, which might be due to an altered stretch receptor input from, for example, areas that are surfactant-depleted and/or partially atelectatic. As PFC might exert a similar effect as surfactant instillation on surfactant-depleted lungs, increased mechanoreceptor discharge during PLV due to increased stretch receptor activity might explain why PNA inhibition occurs at a higher arterial PCO$_2$ during PLV than during GV. This is possibly supported by the fact that administration of surfactant has been shown to increase the activity of mechanoreceptors in surfactant-depleted animals (120).

Higher airway pressures are needed to achieve inhibition of inspiratory activity during GV in animals with surfactant-depleted lungs than in animals with normal lungs. After surfactant depletion, inhibition of inspiratory activity during PLV occurs at about the same peak inspiratory and end-expiratory pressures and tidal volume as during GV. Inhibition of inspiratory activity occurs at a lower arterial pH and a higher arterial PCO$_2$ during PLV than during GV in animals with surfactant-depleted lungs, which can be explained by recruitment of pulmonary stretch receptors during PLV.
Conclusions

The following conclusions can be drawn from the results of the performed investigations:

- Differences in inspiratory pressure waveform influence the spontaneous breathing effort during A/C ventilation in cats. A squarewave inspiratory pressure waveform strongly inhibits spontaneous inspiratory activity. One reason for this inhibition is earlier and sustained peak PSR activity during inspiration.

- The phasic character of PSR activity is similar during GV and PLV.

- PSR activity is not higher during PLV than during GV in cats with healthy lungs. This implies that there is no indication of extensive stretching of the lung during PLV.

- Regulation of breathing is maintained during PAV in surfactant-depleted cats. PSR activity is higher and PNA is lower during PAV than during CPAP both before and after surfactant instillation.

- Inhibition of inspiratory activity occurs at a higher PaCO₂ during PLV than during GV in cats with surfactant-depleted lungs. This could indicate that PLV induces better recruitment of mechanoreceptors than GV.
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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 Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to October, 1985, the series was published under the title “Abstracts of Uppsala Dissertations from the Faculty of Medicine”.)