Breathing Pattern and Lung Mechanics during Assisted Ventilation

Response of Slowly Adapting Pulmonary Stretch Receptors and Effects on Phrenic Nerve Activity in Cats with Normal and Surfactant Depleted Lungs

BY

RICHARD SINDELAR
Regulation of Breathing and Lung Mechanics during Assisted Ventilation

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ABSTRACT

Different modes of assisted ventilation were investigated in cats before and after lung lavage and after instillation of surfactant. The activity of single units of slowly adapting pulmonary stretch receptors (PSRs) in the vagal nerve and the integrated phrenic nerve activity were recorded. The instantaneous impulse frequency ($f_{imp}$) of PSRs was calculated and related to transpulmonary pressure ($P_{tp}$), tidal volume ($V_t$) and the calculated energy storage of the lung ($\Sigma P*\Delta V$). Respiratory rate (RR), inspiratory and expiratory time, and $V_t$ were measured, and their coefficients of variation were calculated.

During assist control (A/C) ventilation with different pressure waveforms, PNA was shorter and lower in amplitude with squarewave pressure waveform than with linear and sinusoidal pressure waveforms in cats with normal lungs, concomitantly with earlier peak $f_{imp}$ during inspiration and prolonged $f_{imp}$ during expiration. The type of pressure waveform can thus influence the spontaneous breathing effort during A/C ventilation.

Proportional assist ventilation (PAV) is a new mode of assisted ventilation which servo-controls the applied airway pressure continuously in proportion to the breathing effort. After lung lavage and surfactant instillation, PAV improves ventilation markedly, with lower PNA and oesophageal pressure deflection and higher RR and variability of breathing, compared to CPAP. In addition, an earlier and higher maximal $f_{imp}$ was observed during PAV. Under conditions of low work and maintained control of breathing, PAV seems to be an attractive mode of ventilatory support.

Low-threshold (LT) and high-threshold (HT) PSRs respond to the surfactant content of the lung partly independent of $P_{tp}$ and $V_t$ in spontaneously breathing cats, implying a possible effect of surfactant on PSRs. The PSR $f_{imp}$ normalized to $\Sigma P*\Delta V$ confirmed these findings and showed that LT and HT PSRs are intrinsically the same. After instillation of surfactant, compliance and PSR activity increased, but the breathing still remained shallow and rapid, suggesting a control of breathing less dominated by PSR activity.

Key words: slowly adapting pulmonary stretch receptor, phrenic nerve activity, assisted ventilation, surfactant, breathing pattern.

Richard Sindelar, Departments of Women’s and Children’s Health, and Department of Physiology, Uppsala University, University Children’s Hospital, SE-751 85 Uppsala, Sweden

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“…and [I shall] make some other experiments, which, I hope, will thoroughly discover the Genuine use of Respiration; and afterwards consider of what benefit this may be to Mankind.”

-Robert Hooke, 1667

Hopefully to the Benefit of Newborn Infants
This thesis is based on the papers listed below, which are referred to in the text by the following Roman numerals:


*The two first authors contributed equally to this work.

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ABBREVIATIONS

A/C assist control ventilation
BPD bronchopulmonary dysplasia
CPAP continuous positive airway pressure
$C_r$ respiratory system compliance
$E_{TOT}$ total system elastance
$E_V$ elastance of the ventilator
$E_L$ elastance of the lung
EMG electromyography
ETT endotracheal tube
$F_iO_2$ inspiratory fraction of oxygen
$f_N$ instantaneous impulse frequency normalized to calculated energy storage of the lung
$f_{imp}$ instantaneous impulse frequency
FRC functional residual capacity
HMD hyaline membrane diseases
HT high-threshold
IRDS idiopathic respiratory distress syndrome
IMV intermittent mandatory ventilation
LT low-threshold
$P_{tp}$ transpulmonary pressure
PAV proportional assist ventilation
PNA phrenic nerve activity
PSR slowly adapting pulmonary stretch receptor
PTV patient-triggered ventilation
$R_{TOT}$ total system resistance
$R_V$ resistance of the ventilator
$R_L$ resistance of the lung
$R_{ETT}$ resistance of the endotracheal tube
RAR rapidly adapting pulmonary stretch receptor
SIMV synchronized intermittent mandatory ventilation
$V_t$ tidal volume
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INTRODUCTION

The combination of antenatal corticosteroids (Liggins and Howie, 1972; Ballard, 1986; Ryan and Finer, 1995), surfactant treatment (Fujiwara et al, 1980; Corbet et al, 1991; Robertson et al, 1992; Jobe, 1993) and new ventilatory techniques has improved the outcome for premature infants and reduced their morbidity (Wegman, 1994). The most widely accepted way to ventilate these infants is to use pressure-limited intermittent mandatory ventilation (IMV), which allows the patient to breathe spontaneously in between mandatory set mechanical breaths with a pre-set frequency (Kirby et al, 1971; Kirby, 1977), preferably at a rate of ≥ 60/min and with a pre-set positive end-expiratory pressure (PEEP) (Jonzon et al, 1971), which inhibits the spontaneous breathing in the early phase of neonatal lung disease (Bland and Sedin, 1983; Sedin, 1986). The disadvantage of IMV is that mechanical breaths may be asynchronous with spontaneous breaths, causing active expiratory efforts against the ventilator (Field et al, 1986), and thereby increasing the risk of barotrauma (Greenough et al, 1983; Clifford et al, 1988), suboptimal gas exchange (Henry et al, 1979; Stark et al, 1978) and cerebral blood flow fluctuations (Rennie et al, 1987).

To prevent these adverse effects of asynchrony during IMV, different methods have been devised (Heldt and Bernstein, 1994) to trigger the mechanical breaths of the ventilator by the spontaneous inspiratory effort of the patient - so called patient-triggered ventilation (PTV).

The triggered mechanical lung inflations during PTV inevitably interact with a variety of respiratory reflexes (Greenough et al, 1983), such as the Hering Breuer inspiratory inhibitory reflex (Hering and Breuer, 1868), thereby affecting the spontaneous breathing effort during PTV. The Hering Breuer inspiratory inhibitory reflex is believed to be mediated by vagal afferents from slowly adapting pulmonary stretch receptors (PSRs) in the lung and shows a stronger response in newborn infants than in adults (Widdicombe, 1961; Rabbette et al, 1994).
REGULATION OF BREATHING

In 1812, Legallois reported that rhythmic breathing in animals persisted after removal of the brain and the cerebellum, but ceased when the medulla was removed. Since then the origin and organisation of the medullary situated respiratory pattern generator, i.e. the central inspiratory activator (Cohen, 1979; von Euler, 1983), have been studied extensively, with respect to a variety of central and peripheral influences.

The central chemoreceptors have been shown to respond relatively slowly but strongly to changes in pH and pCO₂ in the cerebrospinal fluid, and more so as a consequence of respiratory than metabolic acidosis, stimulating an increased ventilation (Leusen, 1950; Leusen, 1954; Mitchell et al, 1963; Fencel et al, 1966; Schlafke et al, 1975; Soto et al, 1991; Corfield et al, 1995). A non-voluntary input to the central inspiratory activator from the pontine pneumotaxic centre synchronizes with inspiration and expiration and thereby possibly contributes to the control of respiratory rhythm (Bianchi et al, 1995), while a voluntary input from the cerebral cortex can oppose the normal regulation of breathing (Horn and Waldrop, 1998).

The peripheral chemoreceptors located in the carotid bodies respond faster but somewhat weaker than the central chemoreceptors to changes in arterial PaCO₂, PaO₂ and pH, whether it is an effect of respiratory or metabolic acidosis (de Castro, 1926; Heymans et al, 1930; McDonald, 1981; Mohan and Duffin, 1997). Peripheral chemoreceptors are also sensitive to the breath by breath alterations in PaCO₂ thereby responding to the rate of change in PaCO₂ during normal tidal breathing (Purves, 1966; Band et al, 1969; Ponte and Purves, 1974). Although it can be derived from these studies that central and peripheral chemoreceptors differ in strength in stimulating or inhibiting ventilation, differences in timing suggest that they complement on another in response to changes in arterial blood gases in both in situations of derangement and during normal breathing.
Pulmonary receptors

Other peripheral inputs to the central inspiratory activator include those from vagal afferents carrying information from pulmonary receptors that respond to inflation and deflation of the lung but also to different chemical agents. The impulses are mediated through myelinated and non-myelinated fibres, and the receptor activity from myelinated fibres is either activity arising from slowly adapting or from rapidly adapting pulmonary stretch receptors, according to their discharge pattern during lung inflations. Whereas PSRs have a regular discharge rate in relation to tidal changes in volume or pressure, RARs have an irregular discharge pattern occurring usually at high airflow or at end inspiration (Sant’Ambrogio, 1982). Another way to distinguish PSRs from RARs is to observe their response to a maintained inflation. PSRs respond with a steady rate (Figure 1) and RARs respond with a fast loss of activity with irregular interspike intervals (Widdicombe, 1954; Davis, 1956).

RARs appear to be located in larger airways, especially in the hilar region, and they respond to probing (touching) of superficial layers of the airway mucosa (Widdicombe, 1954). RARs have also been called “irritant receptors”, as they respond to different inhaled irritants as suggested by their superficial location. It has also been proposed that they contribute to eliciting the cough reflex (Korpas and Tomori, 1979). Several authors have also shown that the activity of RARs are inversely related to lung compliance (Sellick and Widdicombe, 1970; Jonzon et al, 1986). It has been suggested that the Hering Breuer deflation reflex, which aims to end expiration and start inspiration, is associated with the activity of RARs, as these receptors respond to deflation with increased activity (Sellick and Widdicombe, 1970), but the deflation reflex has also been found to be associated with the activity in nonmyelinated fibres i.e. C fibres, during vagal cooling (Jonzon et al, 1988; Head, 1889; see Head’s paradoxical reflex page ?). The C fibres, or otherwise called J receptors, outnumbers the myelinated fibres
The raw nerve activity of slowly adapting pulmonary stretch receptor (PSR) during positive pressure ventilation with a squarewave pressure waveform, related to airflow and tidal volume (Vt). A.U. = arbitrary units. Paw = airway pressure.
in the lung by 3:1 (Agostoni et al., 1957), but their part in the respiratory control still awaits a clear definition. In the early 1950s Paintal (1953) observed in cats that injection of phenyldiguanide into the right atrium evoked C fibre activity of the vagal nerve. Since then, Coleridge and Coleridge (1984) have succeeded to classify them into bronchial and pulmonary C fibres according to their circulatory accessibility through either the bronchial or the pulmonary circulation. Also differences in mechanosensitivity, and chemosensitivity to exogenous chemicals or endogenous substances, has been observed (Kaufman et al., 1980; Coleridge et al., 1978). One way to differentiate the activity in nonmyelinated fibres from the activity in myelinated fibres, is to do a graded cooling of the vagal nerve, by which the activity in myelinated fibres will be inhibited. This method was applied by Hammouda and Wilson already in 1939, showing an increased breathing frequency and decreased tidal volume. The same breathing pattern was observed by Miserocchi et al. (1978) when RARs and C fibres were stimulated separately by histamine aerosol and intravenous injection of phenyldiguanide. As it seems that these receptors aim either to protect or to improve ventilation under conditions of deranged lung function, they may play a hitherto unknown role in different lung diseases such as idiopathic respiratory distress syndrome and bronchopulmonary dysplasia. Since Hering and Breuer described the inspiratory inhibitory reflex in 1864, it has been believed that this reflex is mediated through the vagal nerve in response to lung inflation, terminating inspiration and starting expiration. This reflex was abolished by bilateral vagotomy, a method later used to investigate the influence of the vagal afferents on the breathing pattern. In 1933 Adrian succeeded in recording PSR activity and relating it to lung volume. Knowlton and Larrabee (1946) showed that the lung volume is not the only factor that influences PSR activity, because inflations with the same volume under conditions of a lower compliance (overdistended lung) elicited a higher PSR activity, indicating a stimulatory effect of pressure on PSRs. These observations
were confirmed in relation to transpulmonary changes by Davis et al (1956) in addition to the observations that differences in airway resistance also seemed to influence PSR activity. Keeping the tidal volume and transpulmonary pressure constant, but inflating the lung with different ramp flow inflations, Pack et al (1986) noted an increase in PSR activity in relation to increases in airflow, and from this result in combination with their previous findings (Pack et al, 1981) of increased phrenic nerve activity during increased ramp inflations, they concluded that activity from PSRs seems to have not merely an inhibitory effect on the breathing effort but also a modulating effect on the control of breathing. In their study of PSRs, Pack et al (1986) categorized the PSRs into high-threshold and low-threshold types in accordance with Ravi (1986), who reported that HT PSRs are more common in small airways and LT PSRs in larger airways (Figure 2). The effect of airflow inflation was more marked with HT PSRs (Pack et al, 1986)

The observation that PSRs modulate the breathing effort is consistent with the results of studies in the 1950s of vagal cooling and vagotomy in relation to work of breathing (Lim et al, 1958; Zechman et al, 1958), which showed that vagal afferents have an important role in optimizing the mechanics of breathing in order to obtain the least costly breathing effort in relation to a certain level of ventilation. Rohrer (1925) and later Otis & Fenn & Rahn (1950) came to the conclusion that a particular frequency of breathing for a given alveolar ventilation gives the least respiratory work, and they suggested that this is “an example of the principle of minimum effort by which many of the body functions seem to be regulated”. Supported by Mead in 1960, he concluded from studies of animals and man at rest that the principal site of the sensory end of the control mechanism for this optimal work of breathing is in the lung.

In 1972 Clark and von Euler demonstrated the inverse relation between inspired lung volume and inspiratory time, depending on intact vagal nerves, and Cross et al (1980) showed that tidal information during different phases of inspiration
Figure 2.

Example of instantaneous impulse frequency ($f_{imp}$) of a low-threshold (LT) and a high-threshold (HT) slowly adapting pulmonary stretch receptor recorded during spontaneous breathing with continuous positive airway pressure (CPAP) in cats with normal lungs. Simultaneous recordings of airway pressure (Paw), tidal volume (Vt) and oesophageal pressure (Poes). Note the end-expiratory of the LT PSR. A.U. = arbitrary units.
and expiration influenced the ongoing breathing effort recorded as phrenic nerve activity. Whereas the activity from central and peripheral chemoreceptors influences the central inspiratory activator, it seems that switching from inspiration to expiration (gating mechanism; Hildebrandt, 1977) is determined primarily by vagal afferents and specifically by PSRs, as shown by experiments of vagal electrical stimulation at an amplitude and a frequency comparable to the temporal summation of PSR activity during different phases of inspiration and expiration (Zuperku et al, 1982; Cohen, 1971; Cohen, 1979). Although other inspiratory and expiratory neural activities exist, it has been useful to record the integrated phrenic nerve activity in these experiments (Figure 3) as an indicator of central respiratory activity.

SURFACTANT

In 1929, von Neergard showed that a lung completely filled with water had an elastic recoil that was much lower than when the lung was filled with air, and concluded that the elastic recoil was attributable largely to surface tension at the air-water interface lining of the alveoli and to a much lesser extent to the elastin fibres in the lung parenchyma. Von Neergard proposed that the retractive forces of the alveolar lining fluid would increase at low lung volumes and decrease at high lung volumes in accordance with the Laplace equation $P = \frac{2T}{r}$ where $P =$ pressure, $T =$ surface tension and $r =$ radius, an assumption which incidentally he found not to be the case, concluding that the surface tension of the alveolar lining must be low and that it must be variable.

In 1955 Pattle expressed his opinion that the surface tension of foam and bubbles arising from the lung must be low, as the bubbles were more stable than those produced by plasma and transudate. Pattle deduced that the bubbles from the lung were lined with a substance which he thought derived from the internal surface of the lung, and suggested that this substance could be absent in the lungs of premature infants, causing atelectasis and hyaline membrane
Figure 3.

Schematic drawing of the integrated phrenic nerve activity (PNA) as calculated from the raw phrenic nerve activity. The mean PNA was measured as the amplitude (h) divided by the duration (l).
(From Norsted T: Inhibition and stimulation of inspiratory activity. Dissertation from the Faculty of Medicine, Uppsala University, 1988).
disease (HMD). These observations were followed by careful studies by Clements (1957) and Brown (1957) of the extracted substance from the lungs, which they mixed with saline. The substance was located on the surface of this mixture and they were consequently able to measure the tensile property of this layer with the Langmuir-Wilhelmy balance method, which is a trough whose area can be made to change with a floating bar, and a platinum strip connected to a torsion balance, detecting the surface tension by touching the surface of the fluid in the trough (see Figure 4 A). They found a decreased surface tension if the surface area was small, and an increased tension if the layer was dispersed over a larger area, thereby they described the relation between surface tension and surface area (see Figure 4 B). With the same method, Avery and Mead (1959) observed a higher surface tension in lung extracts from premature infants with HMD, suggesting a deficiency of the surface active substance in these infants.

During the 1960s and early 1970s it was discovered that surfactant is composed of about 80% phospholipids, 8% neutral lipids and 12% proteins, and that these proteins play an essential role in improving the surface properties of surfactant and regulating the surfactant secretion and uptake of type II pneumocytes (King and Clements, 1972; Phizakerley et al, 1979; King, 1984; Wright and Clements, 1987; Possmayer, 1990). The composition of surfactant isolated from healthy mammals by lung lavage is fairly constant (King, 1984), as also is the alveolar surfactant pool of the newborns of these species, in the order of 100 mg/kg (Jobe and Gluck, 1979; Jobe et al, 1983; Jackson et al, 1984; Jobe and Jacobs, 1984).

In 1972, Enhörning and Robertson demonstrated that in a model of surfactant deficiency in premature rabbits exogenous instillation of surfactant resulted in improved lung expansion. Similar observations were shown in premature lambs (Ikegami, 1981), and these were followed by studies of the other most commonly used model of surfactant deficiency, namely repeated lung lavage with saline (Ikegami et al, 1979; Lachmann and Robertson, 1982; Bremel and
Figure 4.

A. The Langmuir-Wilhelmy trough with a torsion balance that measures surface tension as a function of changes in surface area.

B. The surface area and surface tension curve showing an increase in surface area (=inspiration) and decrease in surface area (=expiration) in relation to the measured surface tension.

The similarities between surfactants from different mammalian species were a prerequisite for using natural surfactant in the treatment of human newborn infants with RDS. In 1980, Fujiwara et al successfully demonstrated for the first time the clinical potential of surfactant treatment of RDS in ventilated newborn infants, using surfactant prepared from bovine lung extracts.

The most consistent response to surfactant instillation in the treatment of newborn infants for RDS is the improved oxygenation (Fujiwara et al, 1980; Shapiro et al, 1985; Davies et al, 1988; Goldsmith et al, 1991). Morphometrical and radiographical studies showed more uniformly inflated lungs (Fujiwara, 1984; Edward et al, 1985), and the pressure-volume curves showed a reduction in the opening pressure, an increased lung volume and stabilization of the lung during deflation (Fujiwara, 1984; Rider et al, 1992; Goldsmith et al, 1991). As both the maximal volume and the volume at the end of deflation increased after surfactant instillation, yielding a net shift upwards of the pressure-volume curve, compliance was not always improved during mechanical ventilation in terms of an increased slope of the pressure-volume curve. Davis et al (1988) reported no change in compliance during mechanical breaths after surfactant treatment of premature infants with RDS, but measurements made during spontaneous breathing revealed improved compliance. The increase in lung volume after instillation of surfactant is partly due to an increased functional residual capacity, as reported by several authors (Robertson and Lachmann, 1988; Edberg et al, 1990; Goldsmith et al, 1991), but contrary to the belief that surfactant instillation will restore lung mechanics to normal, it seems that this increase in lung volume is related to increased distension of alveoli rather than to alveolar recruitment (Goldsmith et al, 1991; Björklund et al, 1996).

Furthermore, the assumed cause of surfactant deficiency in the pathogenesis of RDS should theoretically be effectively treated with surfactant instillation of an amount equal to the surfactant pool of newborns (≈100 mg/kg). However, it
seems that exogenous surfactant does not prevent RDS, but only decreases its incidence and severity (Jobe and Ikegami, 1987), suggesting that other factors influence the course of RDS, among which lung immaturity probably plays an important role. Also, a variety of substances interfere with the secretion and function of surfactant, such as protein and red cell debris in oedema fluid, and meconium aspiration (Ikegami, 1994). However, surfactant treatment of RDS has been shown to reduce air leaks (pneumothorax and pulmonary interstitial emphysema), the incidence of BPD, and thereby the mortality from RDS (Enhörning et al, 1985; Merritt et al, 1986, Dunn et al, 1991; Fujiwara et al, 1990; Speer et al, 1992).

**LUNG MECHANICS**

**Surface tension and elastic recoil related to energy storage and work of breathing**

The hysteresis in the pressure-volume curve shows remarkable resemblance to that in the surface area-surface tension curve as measured with the Langmuir-Wilhelmy balance method (Figure 4 and 5) (Mead et al, 1970), suggesting that the alveoli play a prominent role in contributing to the elastic recoil pressure of the lung during tidal breathing. Elastic recoil pressure is determined by the sum of tensions in the lung tissue, i.e. collagen, elastin and the surface tension at the interface of the air surface of the alveoli (Mead et al, 1970). Collagen and elastin are the main elastic elements of the lung (Pierce and Ebert, 1965; Adamson, 1968), but collagen is less distensible than elastin (Stromberg and Weiderhielm, 1969; Carton et al, 1962). A study of their separate contributions to the elastic recoil pressure in the liquid-filled lung, a method which eliminates the surface interfacial tension activity, showed increased compliance at low and medium lung volume ranges when elastin was destroyed, and increased compliance at high lung volumes when collagen was destroyed (Karlinsky et al, 1976). These findings support the model proposed by Setnikar and Meschia (1953), in which elastin dominates tissue forces at low and medium lung volume ranges, and
Figure 5.

The pressure-volume curve. Arrows show the direction of inspiration and expiration. The line between A-C is the pressure-volume slope i.e. the compliance curve. The area between A-B-C-A is the work done against airflow resistance during inspiration; A-C-E-A is the work done against elastic recoil during inspiration; A-C-D-A is the frictional resistance during expiration.
collagen dominates tissue forces at high ranges of lung volume. From a study in which the liquid-filled lung was compared with the air-filled lung, whereby the elastic recoil pressure was separated into tissue tension (mainly elastin and collagen) and surface tension (alveolar interface), it was suggested that surface tension is normally the major determinant of elastic recoil at volumes larger than the functional residual capacity (Hoppin and Hildebrandt, 1977). As there might be differences in volume between the liquid- and air-filled lung, Mead et al (1957; 1970) defined the elastic recoil in terms of the density of the elastic elements and the tensile force per unit area transmitted by each of these elements. Another approach to these geometrical assumptions was proposed by Wilson (1981), who suggested that mechanical energy is conserved as lung volume changes, and that the difference between energy stored in liquid- and air-filled lungs is the sum of surface energy and the energy of tissue distortion caused by surface tension, the tissue distortion increasing with increased lung volume. In a further attempt to separate the elements of tissue tension and surface tension in lung distensibility, Haber et al (1983) concluded that although tissue elements (mainly elastin and collagen) provide a degree of structural rigidity for alveolar septa and facilitate the transmission of forces between air spaces, tissue elastic properties do not normally determine the lung distensibility, i.e. the size of air spaces. These observations make it reasonable to estimate the energy storage of lung tissue during inspiration by calculating the area between the pressure-volume slope and the volume axis, which is the pressure times volume divided by two (Figure 5) (Lumb and Nunn, 2000). This area represents the work against the elastic recoil during inspiration. The area between the pressure-volume curve and the slope during inspiration represents the work against airflow resistance (Figure 5). If there was no airflow resistance during inspiration and expiration, the pressure-volume curve would be equal to the pressure-volume slope, and the system would resonate (oscillate) with a frequency related to the inert property of the elastance of the lung (incidentally
this can be simulated with proportional assist ventilation when resistive unloading compensates for the entire resistance of the endotracheal tube and the airways). This might potentially be used for defining the property of lung elasticity in normal lungs and in lung disease.

ASSISTED VENTILATION

During IMV a pre-set mechanical breath is applied by increasing the airway pressure at the end of the endotracheal tube, thereby creating a pressure difference between the airway opening and the alveoli. Airflow is thus directed into the lung until pressure at the airway opening equals the intra-alveolar pressure. The tidal volume attained within the pre-set inspiratory time and at a certain pressure depends on the resistive and elastic properties of the lung (Lumb and Nunn, 2000; Boynton et al, 1994; Goldsmith and Karotkin, 1996).

Continuous positive airway pressure (CPAP)

As early as in 1936, Poulton and Oxon reported the use of positive pressure therapy in the treatment of acute ventilatory insufficiency in patients with lung failure (Poulton and Oxon, 1936). Subsequently continuous positive pressure breathing (CPPB) was used to treat pneumonia (Bullowa, 1937), pulmonary oedema and respiratory obstruction (Barach et al, 1937) and adult respiratory distress syndrome (Ashbaugh et al, 1967). These experiences and the insight gained into the pathophysiology underlying hyaline membrane disease (HMD) i.e. idiopathic respiratory distress syndrome (IRDS) in premature infants (Gitlin and Craig, 1956; Tierny and Johnson, 1965; Taylor and Abrams, 1966; Brumley et al, 1967; Adams et al, 1970), together with the early efforts of recovering and defining the properties of surfactant (Clements et al, 1958; Avery and Mead, 1959; King and Clements, 1972), led to the successful use of CPAP in spontaneously breathing neonates with IRDS by Gregory et al (1971). They reported improved PaO₂ and increased survival in these infants. The beneficial
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effects of CPAP, with increased PaO\textsubscript{2}, have been ascribed to an increase in functional residual capacity (FRC) through the recruitment of collapsed alveoli (Chernick, 1973). This in turn increases the alveolar surface area and improves the ventilation to perfusion ratio, thereby decreasing the intrapulmonary shunt (Chernick, 1973). Besides the above-mentioned benefits, a decrease in total airway resistance during inspiration has been observed during CPAP, in addition to a decreased respiratory rate and tidal volume, with improved regulation of breathing, but also a decrease in lung compliance has been reported (Saunders et al, 1976). In addition, Lawson et al (1979) and Wyszogrodski et al (1975) reported increased release and activation of surfactant. The decrease in compliance (Saunders et al, 1976) might be explained by an overdistension of the lungs, or as a result of applying a too low airway pressure, close to the airway opening pressure, where the alveolar tension is higher in the non-compliant lung according to the Laplace law. If CPAP is applied correctly, this will optimize the compliance curve by shifting it above the airway opening pressure, and consequently decrease the work of breathing. The additional redirection of flow to the patient during inspiration reduces further the work of breathing during inspiration by reducing the work performed against air flow resistance (Katz et al, 1985). The regularization of the breathing pattern, with a reduced respiratory rate (Thibeault et al, 1977; Martin et al, 1977) and a reduced frequency of apnoeic episodes (Speidel and Dunn, 1976; Kattwinkel et al, 1976), has been explained by the supposed stabilization of alveoli, increased oxygenation, and stimulation or inhibition of pulmonary reflexes (Jonzon and Sedin, 1982; Miller et al, 1990). These reflexes might be mediated by afferent nerve activity in the vagal nerve as described by Norsted et al (1985). The same authors (Norsted et al, 1985) reported an increased impulse frequency of the afferent vagal nerve activity during inspiration and expiration, concurrently with an increase in the mean activity of the integrated phrenic nerve activity; this activity became more regular during CPAP, while its duration was shorter when
the vagal nerve was intact, giving a longer expiration and consequently a
decreased inspiratory to expiratory ratio (see further explanation under “Phrenic
nerve activity”). Similar observations were explained by Martin et al (1977) as
the stimulatory effect of increased FRC during CPAP on the Hering Breuer
inspiratory inhibitory reflex (see further “Hering Breuer reflex”) with prolonged
expiratory time.

PATIENT-TRIGGERED VENTILATION (PTV) –
Assist control ventilation (A/C) and synchronised intermittent mandatory
ventilation (SIMV)
With the increased use of mechanical ventilation of newborn and especially
preterm infants in the late 1960s and early 1970s, it soon became obvious that
long-term exposure to positive pressure ventilation and a high inspiratory
fraction of oxygen ($F_{I\text{O}_2}$) caused adverse side-effects such as bronchopulmonary
dysplasia (BPD) (Northway et al, 1967; Bruce et al, 1992). Furthermore,
asynchrony between spontaneous and mechanical breaths could cause
barotrauma, i.e. pulmonary air leaks (Greenough et al 1983; Greenough et al,
1984), fluctuations in cerebral blood flow with a concomitant risk of
periventricular haemorrhage (Perlman et al, 1985; Rennie et al, 1987), and
suboptimal ventilation and oxygenation, necessitating a further increase in
ventilatory pressures (Henry et al, 1979). Efforts were made to change the
settings of mechanical ventilation during IMV in order to suppress the
spontaneous breathing efforts or to entrain these with the ventilator (Field et al,
relaxants were associated with a reduction in the incidence of pneumothorax in
ventilated premature infants, and Pollitzer et al (1981) noted that muscle
relaxants led to a faster recovery in ventilated infants with IRDS. On the other
hand, there are numerous reports of adverse effects of analgesia and muscle
relaxants during ventilation of infants, including delayed weaning and a longer
duration of ventilation, lower lung volumes due to reduced FRC, a need of a higher mean alveolar pressure and of increased F\textsubscript{1}O\textsubscript{2}, and reduced venous return and cardiac output (Runkle and Bancalari, 1984; Miller et al, 1994). Attention has therefore been focused on different ventilatory systems in which the mechanical breaths are triggered by the spontaneous inspiration, i.e. PTV. The two most frequently employed modes of PTV are assist-control (A/C) ventilation, whereby every spontaneous breath triggers the ventilator, and synchronized intermittent mandatory ventilation (SIMV), whereby the ventilator is triggered by selected spontaneous breaths so as to control the ventilator rate (Heldt and Bernstein, 1994). It has been a challenge to devise sensors for the detection of inspiratory effort in these small infants, and some problems still remain unsolved. The type of sensors used, detect changes in airway flow, airway pressure, impedance of the chest, or movement of the abdomen (Bernstein et al, 1993; Heldt and Bernstein, 1994; Donn et al, 1994; Greenough et al, 1991; Visveshwara et al, 1991; Cleary et al, 1995). Compared to IMV, studies of PTV have shown improved oxygenation (SIMV: Cleary et al, 1995), increased and more consistent tidal volumes (SIMV: Bernstein et al, 1994), decreased fluctuation in cerebral blood flow (SIMV: Govindaswami et al, 1993), and decreased work of breathing (A/C: Jarreau et al, 1996). Delayed trigger timing, missed spontaneous breaths, triggering on expiration or inappropriate triggering, i.e. autocycling due to artefactual signals, are some of the problems encountered with the different devices for triggering (Heldt and Bernstein, 1994). Another problem is the interaction between the spontaneous breathing effort and the setting of the mechanical breath, which might interfere with pulmonary reflexes that modify the control of breathing. In this respect, the occurrence and the extension of the pre-set mechanical breath in the spontaneous respiratory cycle might stimulate some of the observed reflexes of newborn infants, such as the Hering Breuer inspiratory inhibitory reflex and Head’s paradoxical reflex, i.e. inspiratory gasping followed by apnoea (Cross et
Also described in infants is a reflex thought to be mediated by chest wall distortion producing a shorter inspiratory time and an increased respiratory rate (Hagan et al, 1977). The studies of human infants have predominantly dealt with different occlusion techniques, either at end-inspiration (De Winter et al, 1995) or at end-expiration (Kirkpatrick et al, 1976), and have indicated an increase in the “strength” of the Hering Breuer reflex in terms of prolonged expiration in premature infants with IRDS compared to term infants (De Winter et al, 1995) and prolonged inspiration in premature infants compared to term infants (Kirkpatrick et al, 1976). Also of interest in this context is that Head’s paradoxical reflex was elicited in rabbits during recovery from vagal cooling below +8°C (Head, 1889) i.e. at a temperature where most of the myelinated fibres (PSRs and RARs) are inactivated, suggesting that non-myelinated fibres, i.e. C fibres are carriers of the afferent information on lung inflation during this reflex (Coleridge and Coleridge, 1984). As the C fibres seem to be activated under extreme conditions such as pulmonary embolism, pulmonary congestion and inflammation (Coleridge and Coleridge, 1975; Paintal, 1973; Frankstein and Sergeeva, 1966) they could play a hitherto unknown part in the control of breathing during PTV in newborn infants with different lung diseases such as RDS and bronchopulmonary dysplasia (Tooley, 1979).

**PROPORTIONAL ASSIST VENTILATION (PAV)**

During A/C ventilation, a pre-set mechanical breath with a defined inspiratory duration, peak inspiratory pressure and positive end-expiratory pressure is triggered by the spontaneous breathing effort as sensed by the ventilator. The patient can thus control the respiratory frequency above the set back-up frequency of the ventilator. In contrast, PAV provides an assistant ventilator pressure proportional to the spontaneous breathing effort throughout the respiratory cycle (Schaller and Schulze, 1991; Schulze and Schaller, 1997),
allowing the patient to fully control the amplitude and timing of each breath. The ventilator counterbalances the elastic forces and/or the airway resistive forces of the lung by instantaneously adjusting the airway pressure proportionally to the calculated volume signal (elastic unloading) and/or to the airflow signal (resistive unloading) as measured by a sensitive pneumotachograph (Schaller et al, 1985) connected to the endotracheal tube. The servocontrol of ventilator pressure proportional to the breathing effort is accomplished by the rapid computing of the airflow signal in the ventilator (<10 ms) in order to keep \( \Delta P/\Delta V \) constant (\( \Delta P = \) airway pressure adjusted continually by the ventilator; \( \Delta V = \) volume calculated by the ventilator from the integrated airflow at the endotracheal tube). The elements of the total system elastance \( (E_{TOT}) \) are the elastance of the lung \( (E_L) \) and the elastance of the ventilator \( (E_V) \), where the set \( E_V \) is negative during elastic unloading:

\[
E_{TOT} = E_L + E_V \quad (E_{TOT} < E_L)
\]

This implies than an increased \( E_L \) in a low-compliant lung (compliance of the lung = \( 1 / E_L \)), is compensated for in the system by an increased negative \( E_V \), in order to attain an \( E_{TOT} \) near the supposed elastance of a normal lung. The result is a lower inspiratory oesophageal pressure deflection for any given increase in lung volume (Figure 6), and the pressure-volume slope (the combined compliance of the lung and the ventilator) will be steeper (Figure 7) and closer to the compliance curve of a normal lung.

Therefore, a higher (lower) inspiratory breathing effort will generate a higher (lower) inspiratory airflow, and consequently a higher (lower) tidal volume, proportionally unloaded by a higher (lower) adjustment of the ventilator pressure, resulting in an increase \( (lower \ increase) \) in the inspired volume (Schulze and Schaller, 1997).

In a similar way the airway resistance can be unloaded in response to the airflow signal, according to the equation \( \Delta P/\text{airflow} = \) constant. Again, the total system resistance \( (R_{TOT}) \), i.e. the combined resistance of the lung airways \( (R_L) \),
Figure 6.

The airway pressure (Paw), tidal volume (Vt), oesophageal pressure (Peos) and phrenic nerve activity (PNA) during continuous positive airway pressure (CPAP) and proportional assist ventilation (PAV). Note immediate decrease in PNA and the decrease in Peos on transition from continuous positive airway pressure (CPAP) to proportional assist ventilation (PAV), showing the combined breathing effort and elastic unloading during PAV.
Figure 7.

The pressure-volume curve, oesophageal pressure and tidal volume during continuous positive airway pressure (CPAP) and proportional assist ventilation (PAV) with elastic unloading. Oesophageal pressure is referenced to atmospheric pressure. The slopes of the pressure-volume curves are the combined compliance of the ventilator-lung system. Note the higher pressure-volume slope during PAV with elastic unloading than during CPAP, and the lower oesophageal pressure with PAV than with CPAP (from Schulze et al, Am J Respir Crit Care Med 153: 671-76, 1996).
ventilator \( (R_V) \) and endotracheal tube \( (R_{\text{ETT}}) \), can be reduced by applying a negative \( R_V \):

\[
R_{\text{TOT}} = R_L + R_V + R_{\text{ETT}} \quad (R_{\text{TOT}} < R_L)
\]

The continually adjusted negative \( R_V \) is the result of the calculated and servo-controlled ratio of \( \Delta P/\text{airflow} \), which is the resistance. Compared to CPAP, the pressure-volume curve during PAV shows a narrowing of the area around the pressure-volume slope (Figure 8), which is a measure of the decrease in the resistive work of breathing.

The most critical factors in the system are the accuracy and reliability of the flow sensor. Increased resistance of the pneumotachograph due to secretion or air humidification, and leakage around non-cuffed endotracheal tubes, are some potential sources of signal error that could affect the success of PAV, especially in subjects with small tidal volumes and air flows.

However, in studies in infants with mild RDS intubated with non-cuffed endotracheal tubes PAV has proved successful in terms of maintained gas exchange with lower transpulmonary pressures compared to A/C ventilation and IMV (Schulze et al, 1999). The same authors have also reported that the effects of elastic unloading on the total compliance of the combined lung and ventilator system can be predicted with high accuracy (Schulze et al, 1993). PAV has been tested in a variety of small animal models, with or without lung injury, and with elastic and/or resistive unloading, demonstrating improved ventilation in comparison to spontaneous breathing with CPAP (Paper I and IV; Schulze et al, 1990; Schulze et al, 1998a; Schulze et al, 1998b). Additionally, studies have shown reduced work of breathing with regard to PNA (Papers I and IV; Schulze et al, 1996; see Figure 6) and to diaphragmatic EMG (Schulze et al, 1995).

There are still questions to be answered such as what gain should be applied in newborn infants with different lung diseases, what end-expiratory pressure is most appropriate under these conditions, and under which conditions elastic unloading should be combined with resistive unloading during inspiration and
Figure 8.

The pressure-volume curve during volume during continuous positive airway pressure (CPAP) and proportional assist ventilation (PAV) with resistive unloading. Note that the loop becomes narrower with resistive unloading both during inspiration and expiration than during CPAP, which is the measure of the decrease in work against airflow resistance during inspiration and expiration (from Schulze et al, Pediatr Res 28: 79-82, 1990)
expiration. It seems that resistance is dependent on the total cross-sectional area of all the airway tubes, the distal and smaller airways contributing less to the total airway resistance (Rodarte and Rehder, 1986; Harris and Wood, 1996). This explains the relatively low airway resistance in newborn infants as compared to adults when related to lung volume, i.e. the specific airway resistance (Harris and Wood, 1996). Also, inspiratory airflow resistance is lower than expiratory airflow resistance, since the airways naturally dilate during inspiration in normal lungs (Harris and Herrick, 1978; Rodarte and Rehder, 1986), while the opposite can be seen in the stiff BPD lung with peribronchial oedema. These observations should be taken into consideration in future applications of PAV and warrant further clinical studies.
AIMS OF THE PRESENT INVESTIGATION

This thesis concerns aspects of the interaction between spontaneous breathing and different modes of assisted ventilation in cats with normal and surfactant depleted lungs. A further question addressed was the effect of surfactant instillation on the response of slowly adapting pulmonary stretch receptors. The specific aims were:

- to test the efficacy of proportional assist ventilation (PAV), which combines elastic and resistive unloading, as a mode of assisted ventilation in cats with intact breathing control but severe pulmonary parenchymal injury (Paper I);
- to study the breathing pattern during PAV with combined elastic and resistive unloading in young cats before and after lung lavage, and after instillation of surfactant, with respect to changes in phrenic nerve activity (PNA) and the activity of PSRs (Paper IV);
- to examine the effects of squarewave, sinusoidal and linear inspiratory pressure waveforms during pressure-controlled assist/control (A/C) ventilation on the firing pattern of PSRs and PNA in cats with normal lungs (Paper II);
- to study the activity of low-threshold (LT) and high-threshold (HT) PSRs in surfactant depleted lungs of spontaneously breathing young cats on continuous positive airway pressure, before and after instillation of surfactant (Paper III);
- to differentiate between the response of PSRs to changes in lung mechanics and their response to instillation of surfactant by normalizing the PSR activity to the energy storage of the elastic tissue in spontaneously breathing cats (Paper III);
- to determine whether changes in PSR activity could explain the breathing pattern in surfactant depleted cats before and after instillation of surfactant (Paper III)
PRESENT INVESTIGATION

Paper I
Proportional assist ventilation is a new mode of patient-controlled ventilation wherein the applied airway pressure is servo-controlled continuously throughout each spontaneous respiratory cycle and changes in proportion to the patient’s breathing effort, allowing the patient to control the extent and timing of lung inflation (see further explanation under “Assisted ventilation”). The ventilator can be set to unload a certain proportion of the elastic forces (elastic unloading) needed to inflate a certain amount of volume at a certain level of lung compliance. Additionally, resistive unloading can be applied in combination with elastic unloading, reducing the airflow resistance of the airways and the endotracheal tube if necessary. In this study, PAV was applied with elastic unloading to compensate for 75% of the elastance and with resistive unloading to compensate for the airflow resistance of the endotracheal tube, in cats with severe respiratory failure after lung lavage. PAV was compared with spontaneous breathing with CPAP with the same pre-set end-expiratory pressure. Compared to CPAP, PAV increased the tidal volume by 50% (22.2 ± 5.3 vs. 34.3 ± 7.4 mL; \( p<0.001 \)) decreased \( \text{PaCO}_2 \) (8.99 ± 2.07 vs. 6.63 ± 1.57 kPa; \( p<0.001 \)) and increased arterial pH (7.14 ± 0.04 vs. 7.25 ± 0.06; \( p< 0.001 \)). PNA was significantly lower during PAV, indicating reduced work of breathing during PAV compared to CPAP. Compared to CPAP, PAV with combined elastic and resistive unloading improves ventilation markedly in severely lung-injured cats, with maintained control of breathing.

Paper II
The effects of squarewave, sinusoidal and linear inspiratory pressure waveforms during pressure-controlled A/C ventilation on the firing patterns of PSRs and PNA were examined. A/C ventilation is a patient-triggered ventilatory mode where every spontaneous breath is intended to trigger a pre-set
mechanical inflation, enabling the patient to regulate the rate of breathing. Peak inspiratory pressure, end-expiratory pressure and inspiratory time were the same for all pressure waveforms. There were no differences in arterial blood gases, respiratory rate or tidal volume between the different pressure waveforms. Peak inspiratory PSR activity was the same with all three pressure waveforms (82 ± 17 impulses s⁻¹), but occurred earlier with squarewave than with sinusoidal or linear pressure waveforms (p<0.05). The PNA amplitude was lower and the duration of PNA was shorter with squarewave than with the other two pressure waveforms (p<0.05). It is concluded that a squarewave pressure waveform during pressure-controlled A/C ventilation strongly inhibits spontaneous inspiratory activity in cats, which can be explained by earlier peak PSR activity during inspiration and prolonged PSR activity during expiration. These findings suggest that the type of inspiratory pressure waveform influences the spontaneous breathing effort during pressure-controlled A/C ventilation, where attempts are made to preserve the physiological control of breathing and promote the spontaneous respiratory effort.

**Paper III**

The activities of LT and HT PSRs were compared in spontaneously breathing young cats with CPAP, before and after lung lavage and after instillation of surfactant, and to observe whether the PSRs respond solely to changes in lung mechanics or directly to instillation of surfactant, or both. Furthermore, the effects of PSR activity on the breathing pattern under these three lung conditions were considered. The instantaneous impulse frequencies \( f_{imp} \) of LT and HT PSRs were related to transpulmonary pressure \( P_{tp} \), tidal volume \( V_t \), respiratory system compliance \( C_r \) and inspiratory time. An additional comparative measure was introduced \( f_{imp} \), normalizing \( f_{imp} \) of PSRs to the calculated energy storage of the lungs \( \Sigma P \Delta V \). Before lung lavage a high linear correlation was observed between the \( f_{imp} \) of HT PSRs and \( P_{tp} \), and between the
$f_{\text{imp}}$ of LT PSRs and Vt ($r = 0.84 \pm 0.17$ and $r = 0.87 \pm 0.03$ respectively; ± S.D.). The $f_{\text{imp}}$ of HT and LT PSRs decreased or was lost after lung lavage and increased or reappeared after instillation of surfactant ($38 \pm 10$ vs. $51 \pm 10$ impulses/s; ± S.E.M.; $p<0.01$). Some HT PSRs ceased to discharge after lung lavage, but recovered after instillation of surfactant.

In normal lungs, HT and LT PSRs have the same $f_N$, indicating that they might not be intrinsically different and that their different responses to $V_t$ and $P_{tp}$ could rather reflect their different localizations in the airways. The $f_N$ of all PSRs was lower after lung lavage ($0.30 \pm 0.10$ impulses/L/kPa*10^-4) and was higher after instillation of surfactant compared with the pre-lavage level ($0.43 \pm 0.11$ impulses/L/kPa*10^-4; $p<0.025$). A high inverse linear relationship was observed in cats with normal lungs between $f_N$ of fall HT PSRs and inspiratory time, but not between $f_N$ of LT PSRs and inspiratory time, suggesting a higher dependence of HT PSRs on the rate of change in $P_{tp}$*Vt, that is the rate of delivery of work to the lung tissue. After instillation of surfactant, $C_r$ increased from $2.54 \pm 0.92$ to $3.32 \pm 1.75$ ml/cm H$_2$O (± S.D.; $p<0.01$) and the respiratory rate increased due to a shorter inspiratory time ($p<0.05$) with persistently low Vt ($p<0.05$). The coefficient of variation for Vt increased after lung lavage and remained high after instillation of surfactant ($p<0.05$).

In conclusion, both HT and LT PSRs respond with decreased activity after lung lavage and with increased activity after instillation of surfactant. These changes in receptor activity are only partly related to $P_{tp}$ and Vt, and a possible direct effect of surfactant on PSRs cannot therefore be excluded. The breathing pattern remained rapid and shallow after instillation of surfactant even though there was an increase in $C_r$ and PSR activity, suggesting a control of breathing less dominated by PSR activity.
The breathing pattern during PAV and CPAP was evaluated in surfactant depleted cats before and after instillation of surfactant. Simultaneous recordings of PNA and activity from single units of PSRs were made. PSR activity was related to $P_{tp}$. Tidal volume ($V_t$) and maximal oesophageal pressure deflection ($\Delta P_{eos}$) were measured. Respiratory rate and inspiratory and expiratory time were calculated, as well as the C.V. for each of these variables. Before lung lavage no major difference was detected between CPAP and PAV in any of the measured variables. Respiratory system compliance decreased by 57% after lung lavage, and increased by 36% after instillation of surfactant. After lung lavage, PAV gave a larger $V_t$, a lower $\Delta P_{eos}$ and a higher RR than CPAP ($p<0.01$), and also a lower amplitude and shorter duration of PNA ($p<0.01$), and a shorter inspiratory time ($p<0.02$). The coefficient of variation for RR was higher during PAV than during CPAP ($p<0.01$), as a result of a higher C.V. for expiratory time ($p<0.02$). After instillation of surfactant, $V_t$ and RR remained higher and $\Delta P_{eos}$ remained lower with PAV than with CPAP ($p<0.05$). The duration of PNA remained shorter and the mean PNA was lower ($p<0.01$ for each) with PAV than with CPAP. No difference in C.V. between PAV and CPAP was detected. The maximal $f_{imp}$ of PSRs was higher and appeared earlier in inspiration during PAV than during CPAP both after lung lavage and after instillation of surfactant ($p<0.01$ for each). The maximal $f_{imp}$ of PSRs was higher during PAV than during CPAP in the recordings after lung lavage and after surfactant instillation ($p<0.01$ for each). There was no difference between PSR $f_{imp}$ in relation to $P_{tp}$ during PAV and that during CPAP in any of the recordings before or after lung lavage, or after surfactant instillation.

In conclusion, the variability of the breathing pattern after lung lavage was greater during PAV than during CPAP, and the depth and rate of breathing were higher, with lower PNA and $\Delta P_{eos}$ during PAV. Both after lung lavage and after surfactant instillation, an earlier and higher maximal $f_{imp}$ was seen during PAV.
than during CPAP. PAV seems to be an attractive mode of ventilatory support under conditions of a low $\Delta P_{\text{eos}}$, low work of breathing and maintained control of breathing.

**CLINICAL IMPLICATIONS**

We have shown that PAV is an effective ventilatory mode in subjects with severe pulmonary injury, maintaining the control of breathing intact in the presence of negative pulmonary pressures. PAV could thereby potentially reduce the risk of barotrauma and shortens the duration of ventilatory support, and facilitate the process of weaning during the early phase of severe lung injury.

One of the mechanisms for maintaining the control of breathing during PAV could be the activity of slowly adapting pulmonary stretch receptors, which seem to work in combination with the ventilator in keeping the breathing effort optimal. Questions still remain to be answered, however, such as what combination of unloading should be applied under which conditions of lung disease.

New ventilators offer the option to choose between different pressure waveforms. We have demonstrated different inhibitory effects of three types of pressure waveform on phrenic nerve activity. The squarewave pressure waveform exhibits the strongest inhibitory effect on PNA during assist control ventilation. When the optimal ventilatory settings are combined in order to improve the possibility of applying patient-triggered ventilation, it seems that sinusoidal and linear pressure waveforms allow for a higher inspiratory effort than the squarewave pressure waveform, thereby increasing the possibility of successful triggering and faster weaning off the ventilator.

In a model of IRDS we have shown that one important modulator system of spontaneous breathing, i.e. slowly adapting stretch receptors, displays lower
activity in this disease than that in healthy lungs. Following treatment with surfactant, PSRs increase their activity partly independently of lung mechanics, indicating a possible direct effect of surfactant on a receptor system, which until now has been considered to respond only to changes in volume and pressure. This could imply a therapeutic possibility of improving the activity of PSRs and thereby the pattern of breathing during recovery.

It is possible that other pulmonary receptors might influence the breathing pattern after lavage and after surfactant instillation, indicating the importance of considering other possible pathways for the pathophysiology of lung disease such as IRDS.

In one study (Paper III) we propose a new approach to studies of the activity of PSRs, by relating their activity to the energy storage of the lung during inspiration. All receptors showed the same normalized value in the healthy lung. The normalized value was lower after than before surfactant instillation. This could imply that PSRs reflect the energy storage of the lung as supplied by the inspiratory work against elastic recoil, and thereby optimising the work of breathing. The regulatory system is altered after lung lavage, with a different breathing pattern, which might contribute to or can be a consequence of an uneven ventilation and thereby the failing distribution of forces and energy within the lung, with tissue damage as a consequence. Also, this could indicate a hierarchy in the control mechanism within the lung, where failed PSR activity after lavage may allow more influence of C fibres and RARs on the control of breathing. In this case an optimal work of breathing is probably not attained.
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