Assisted mechanical ventilation using combined elastic and resistive unloading in cats with severe respiratory failure: effects on gas exchange and phrenic nerve activity

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This study tests the efficacy of respiratory mechanical unloading as a mode of assisted mechanical ventilation in cats with an intact breathing-control system but severe pulmonary parenchymal injury. Twelve anaesthetized, intubated cats received multiple saline lung lavages so that their total respiratory system compliance decreased from 56.1 ± 10.4 to 26.8 ± 6.8 ml/kPa (p < 0.001) and their PaO 2 fell to 12.38 ± 4.71 kPa when 100% O 2 was used as inspired gas. They were then exposed to three consecutive 15-min periods of CPAP of 0.5 kPa, respiratory unloading and again CPAP of 0.5 kPa. Unloading was applied with end-expiratory pressure of 0.5 kPa, elastic assistance of 0.03 kPa/ml and resistance compensation of 2.0 kPa/l/s. Arterial blood gases for the CPAP baselines did not differ significantly before and after unloading: pH 7.14 ± 0.04 vs. 7.16 ± 0.06; PaCO 2 8.99 ± 2.07 vs. 8.33 ± 2.01 kPa; PaO 2 12.4 ± 4.7 vs. 13.3 ± 7.6 kPa. Nor did the baselines differ in terms of tidal volume, respiratory rate and phrenic nerve activity. Unloading increased tidal volume substantially by about 50% and increased respiratory rate slightly, while inspiratory time remained unchanged. PaCO 2 fell to 6.63 ± 1.57 kPa and pH rose to 7.25 ± 0.06. Phrenic nerve activity was significantly down-regulated in terms of total number of impulses and mean impulse frequency in the phrenic nerve burst. These results suggest that combined elastic and resistive unloading may be an effective means of assisted mechanical ventilation in severe respiratory failure of pulmonary parenchymal origin.

Conventional controlled mechanical ventilation has been a standard method of care in neonatal and paediatric patients with severe pulmonary parenchymal disease causing respiratory failure. Whenever the control of breathing system remains functional in these patients, regular spontaneous respiratory efforts may interfere with the cycling of the respirator. Such “fighting the ventilator” has been found to be associated with untoward side effects (1). It may lead to an increased use of sedatives and muscle relaxants (2) and prolong the duration of weaning from mechanical ventilation (3). It may also cause the clinician to use borderline hyperventilation to inhibit spontaneous respiratory activity at the expense of possibly increased barotrauma. Patient-triggered ventilation, wherein the patient’s spontaneous breathing effort starts a mechanical breath by initiating a trigger device (4), has been suggested as a solution to the problem of asynchrony. With this technology, a trigger event induces a mechanical cycle that is preset in terms of timing and inflation pressure. These fixed settings, however, may still interfere with the natural rhythm even if a perfect rate match is achieved. Moreover, trigger failure and autotriggering may impose problems (5, 6). Respiratory mechanical unloading is a new method of assisted mechanical ventilation that may overcome some of these problems, as it servocontrols the applied airway pressure continuously on the sole basis of the subject’s respiratory activity. This mode adjusts the applied airway pressure instantaneously in proportion to the patient’s spontaneous inspiratory volume and airflow throughout inspiration in order to allow the subject to fully control the extent and timing of lung inflation. The ventilator thereby enhances the effect of a diaphragmatic effort on ventilation while never imposing an increased pressure without ongoing effort. However, to our knowledge no data are available on the effectiveness of respiratory mechanical unloading in severe
respiratory failure. Furthermore, in most studies on respiratory unloading either resistive unloading alone (7) or elastic unloading alone has been used (8). In order to treat severe respiratory failure effectively with respiratory unloading, it may be necessary, however, to apply both modalities simultaneously so that both the resistive and elastic work of breathing is reduced by the assistance.

We have previously shown that respiratory unloading can safely be applied to small animals with high respiratory rates and small tidal volumes (9, 10). Resistive unloading specifically reduced resistive work of breathing (7) and elastic unloading specifically decreased elastic work of breathing (8). These studies were performed on normal or moderately injured lungs. The animals were able to maintain adequate gas exchange when resistive unloading was applied alone while the elastic work of breathing was left unchanged, or when elastic unloading was applied alone while the resistive work of breathing was left unchanged. These animals remained in a stable cardiorespiratory condition even during 10-min baseline measurements without any type of assisted ventilation, i.e. during application of continuous positive airway pressure (CPAP).

The aim of this study was to test the effectiveness of combined resistive and elastic unloading in a model of severe respiratory failure. In this model, the respiratory failure was due to pulmonary parenchymal damage, while the respiratory control remained intact. We investigated short-term effects of combined unloading on the pattern of breathing, on phrenic nerve activity and on arterial blood gases.

Methods

General

Twelve adult cats (mean body weight 2.72 kg, range 2.3–3.2 kg) were initially anaesthetized with chloroform followed by intravenous administration of 20 ml of 0.72% chloralose (E. Merck AG, Darmstadt, Germany). Catheters were inserted in the femoral vein and femoral artery so that their tips were located within the thorax. The venous catheter was used for administration of supplemental anaesthetic. Blood samples were obtained through the arterial line for intermittent blood gas measurements (Acid-Base Laboratory ABL 300, Radiometer Corp., Denmark). A mixture containing 2/3 of 10% glucose and 1/3 of bicarbonate (50 mg/ml) was given intravenously at a rate of 6.4 ml/h throughout the experiment. Additional doses of chloralose were given regularly during the experiment. The cats were intubated orally with a 3.0 mm ID endotracheal tube and connected to an infant ventilator. A medial incision was made in the pretracheal region and a ligature was tied around the oesophagus to prevent leakage around the tube. During the surgical procedures the animals were kept under pressure-controlled mechanical ventilation with the following settings: peak inspiratory pressure 2 kPa, positive end-expiratory pressure (PEEP) 0.2 kPa, inflation time 1 s, rate 20/min.

An 8 French catheter with an oesophageal balloon (40 × 7.5 mm, flat frequency response up to 5 Hz) was advanced into the lower part of the oesophagus until the largest tidal pressure swing occurred. A ligature was tied around the oesophagus to prevent air from entering the oesophagus.

The left phrenic nerve was exposed and the connective sheath was removed under microscopic control. The intact phrenic nerve was then placed on platinum electrodes. The nerve and the electrodes were immersed in mineral oil.

Lung surfactant depletion was induced by a lavage procedure (11). Warm normal saline solution in an amount of 30 ml/kg was flushed into the lungs at a pressure not exceeding 4.0 kPa, using a funnel connected by a tube to the endotracheal tube. A gentle chest compression was briefly applied to improve the distribution of the lavage fluid, which was then recovered with a suction device. This procedure was repeated seven times. Thereafter the animal was mechanically ventilated for 30 min with the following settings: peak inspiratory pressure 2.0 kPa, PEEP 0.5 kPa, inspiratory time 1.3 s, rate 20/min. A blood sample for arterial blood gas measurement was then taken. The compliance of the total respiratory system (lungs and chest wall) was measured before the lavage and after a 30-min post-lavage stabilization period.

Ventilator

A Stephanie Infant Ventilator (F. Stephan Medizintechnik GmbH, Gackenbach and Dresden, Germany) was used throughout the study. Technical details of this device have been described elsewhere (12). Briefly, it is a servocontrolled system with a sensor for the airway pressure as measured at the endotracheal tube connector and a sensor for airflow. The latter is a pneumotachometer with a resistance of 1.1 kPa/l/s at 5 l/min and a dead space of 0.9 ml (13). This probe is inserted between the endotracheal tube connector and the Y connector of the ventilator tubing circuit. In addition to the conventional modes of mechanical ventilation, the Stephanie Infant Ventilator provides resistive and elastic unloading. To generate resistive unloading, the airflow signal of spontaneous breathing as measured by the ventilator’s airflow sensor is additionally fed into the ventilator’s feedback control loop for airway pressure such that a positive (inspiratory) flow signal increases the airway pressure proportionally and instantaneously. Likewise, a negative (expiratory) flow signal decreases the airway pressure relative to the set “baseline” for airway pressure. This “baseline” is the PEEP that is always re instituted at end-expiration zero flow. During elastic unloading, the volume signal of spontaneous breathing (obtained by digital integration
of the airflow signal) is imposed on the ventilator’s feedback control loop for airway pressure such that the airway pressure increases instantaneously in proportion to the inspired volume. The gain of the proportional change in airway pressure can be adjusted on a continuous scale. The cut-off frequency of the system in the respiratory unloading modes is above 15 Hz. This specifically enables the ventilator to generate the required airway pressure waveforms for respiratory mechanical unloading without a significant phase lag (10). This feature is of critical importance for small subjects with their high respiratory rates.

Measurements

The flow and airway pressure signals as measured at the proximal end of the endotracheal tube were obtained through the analogue outlet of the ventilator. A precision ball flowmeter was used to calibrate the flow signal. Oesophageal pressure was recorded from the oesophageal balloon catheter with a pressure transducer (Druck Ltd., Leicestershire, UK). Both the airway and oesophageal pressure transducers were calibrated using a water manometer as reference. An end-expiration occlusion test was performed to ensure correct recording of the oesophageal pressure (14). Phrenic nerve activity was recorded, amplified and integrated with a Neurolog system (NL 100; NL 103; NL 105; NL 115; NL 200; Digitimer Research Instrumentation Inc., Welwyn Garden City, Hertfordshire, UK). An 8-channelled medical signal amplifier (Hellige, Germany) was connected to a recorder (Hellige 330-P, Germany). The integration of the rectified signal was performed by a resistance-capacitance low-pass filter with a leak. The time constant of this system was 250 ms. A moving time average of phrenic nerve activity was thereby provided.

Data acquisition and processing

The signals of airflow, airway pressure, oesophageal pressure and integrated phrenic nerve activity were digitized online and stored on disks, using a LabVIEW data acquisition system (National Instruments Corp., Austin, TX, USA). The sampling frequency for each waveform was 100 Hz. WINDAQ playback software (DATAQ Instruments, Inc., Akron, Ohio, USA) was used to review, process and analyse the acquired waveforms. Processing included integration of the airflow signal to obtain tidal volume. Total respiratory system compliance was calculated as the quotient of the difference between end-inspiratory pressure and PEEP over tidal volume during pressure-controlled ventilation. The rate of spontaneous breathing was calculated from the time interval between two consecutive starting points of inspiratory airflow. Inspiratory time was measured as the time from the onset of inspiratory airflow to its end. The amplitude of the integrated phrenic nerve activity was used as a measure of the total number of impulses in the phrenic nerve burst. The mean impulse frequency in the phrenic nerve burst was calculated from the amplitude and the duration of the phrenic nerve burst for each recorded breath (15–17). All measurement points were obtained directly from the digitally stored tracings, using the notepad tool of the WINDAQ® playback software. These data were imported in spreadsheets for calculation of derived parameters such as the mean impulse frequency. At least ten breaths were evaluated for each experimental setting.

Protocol

After the 30-min post-lavage stabilization period, each experiment was started with the animal breathing spontaneously over a 15-min period with a CPAP of 0.5 kPa. This baseline was followed by a 15-min epoch of combined respiratory mechanical unloading. During this period, the same end-expiratory pressure was applied. Resistive unloading was set to 2.0 kPa/l/s. Elastic unloading was set to compensate 75% of the respiratory system elastic recoil. This was done by increasing the gain of elastic unloading to 75% of the measured total respiratory system elastance. Finally, a second baseline with 15 min of CPAP was obtained. Thirteen minutes after each change in setting, all signals were recorded over 2 min, after which an arterial blood sample was taken.

In a pilot protocol we attempted to test all three types of respiratory mechanical unloading, i.e. resistive, elastic and combined unloading separately. However, it soon became obvious that the cats were too sick to survive multiple test periods with little respiratory assist. In particular, the inspiratory ventilator pressure during resistive unloading alone was low. In addition we reasoned that testing elastic unloading alone would be of little potential clinical meaning in this disease model because the clinician would attempt to unload a resistive constraint anyway in a comparable clinical situation. These were the reasons for not testing all three modalities separately in the final study protocol. This protocol was approved by the Animal Research Ethics Committee of Uppsala University.

Statistics

One-way repeated measures analysis of variance (ANOVA) was used to test for differences between the first baseline, the ventilatory assistance and the second baseline. Bonferroni t-tests were applied to isolate the differences between the three steps of the experiments whenever a difference was detected by ANOVA. A paired two-tailed t-test was used to compare data before and after surfactant depletion. Unless otherwise indicated, data are given as mean ± standard deviation. p values <0.05 were considered significant.
Results

Saline lung lavage significantly decreased the total respiratory system compliance from 56.1 ± 10.4 to 26.8 ± 6.8 ml/kPa (p < 0.001), i.e. the post-lavage total respiratory system elastance was 0.0397 ± 0.0108 kPa/ml. The lung injury after surfactant depletion was so severe that respiratory acidosis developed in all cats, with arterial pH values < 7.20 within 10 min of unassisted spontaneous breathing at CPAP. The post-lavage PaO₂ values ranged from 6.85 to 20.02 kPa at 100% O₂ breathing with CPAP (Table 1). However, regular spontaneous respiratory activity never ceased during the experiments and the animals maintained strong phrenic nerve activity throughout the protocol, so that prolonged periods of respiratory unloading could be applied without a need to revert to controlled mechanical ventilation for apnoeas.

Respiratory mechanical unloading was applied with negative ventilator elastance of 0.0299 ± 0.0076 kPa/ml (depending on the respiratory system elastance of the individual cats) and negative ventilator resistance of 2 kPa/l/s (in all cats). Signs of resistive overcompensation such as oscillations (18) did not occur with this gain setting, but were immediately observed in all cats when the gain for resistive unloading was slightly further increased. Signs of elastic overcompensation with runaway phenomena (8) did not occur. Combined unloading increased the tidal volume and respiratory rate significantly (Fig. 1), leading to near normal, stable PaCO₂ levels and higher arterial pH values. The mean PaO₂ was highest during unloading, but did not differ statistically from the values at baseline CPAP either before or after the assistance. The total number of phrenic nerve impulses per breath was significantly smaller during unloading. Since the inspiratory time remained unchanged, the mean impulse frequency in the phrenic nerve activity bursts was also lower during unloading. Thus, phrenic nerve activity per breath decreased during unloading (Table 1).

Discussion

This study demonstrates the short-term efficacy of combined elastic and resistive unloading as a mode of assisted mechanical ventilation in a cat model with severe pulmonary parenchymal damage but an intact control of breathing system.

Methodological aspects of the study

Saline lung lavage significantly impaired lung function, as evidenced by a decrease in lung compliance and arterial oxygenation. As the extent of pulmonary function derangement was stable during our experiments, changes in target variables have not been related to a baseline drift over time but can be attributed to the intervention itself. This is clear from the fact that there

| Table 1. Arterial blood gases, pattern of spontaneous breathing, and phrenic nerve activity before, during and after respiratory mechanical unloading in surfactant-depleted cats (n = 12)*. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | CPAP before unloading | Combined elastic and resistive unloading | CPAP after unloading | p (ANOVA)       |
| Arterial pH      | 7.14 ± 0.04      | 7.25 ± 0.06*    | 7.16 ± 0.06      | <0.001          |
| PaCO₂ (kPa)      | 8.99 ± 2.07      | 6.63 ± 1.57*    | 8.33 ± 2.01      | <0.001          |
| PaO₂ (kPa)       | 12.38 ± 4.71     | 16.34 ± 10.86   | 13.28 ± 7.63     | NS              |
| Tidal volume (ml)| 22.24 ± 5.33     | 34.28 ± 7.42*   | 20.02 ± 6.73     | <0.001          |
| Respiratory rate (min⁻¹) | 19.57 ± 4.78 | 22.51 ± 7.07*  | 20.59 ± 5.88     | 0.036           |
| Inspiratory time (s) | 1.14 ± 0.24     | 1.04 ± 0.22     | 1.08 ± 0.23      | NS              |
| Total number of impulses per PNA burst (AU) | 95.2 ± 44.3 | 60.6 ± 20.6* | 90.2 ± 44.3 | 0.009 |
| Mean impulse frequency in PNA burst (AU) | 79.3 ± 34.6 | 61.0 ± 21.1* | 77.9 ± 34.4 | 0.043 |

* AU: arbitrary units; PNA: phrenic nerve activity.

b Significantly different from CPAP before unloading.

c Significantly different from CPAP before unloading and from CPAP after unloading (repeated measures ANOVA, Bonferroni t-tests).

![Fig. 1. Representative tracings of physiological signals for a surfactant-depleted cat during spontaneous breathing at continuous positive airway pressure of 0.5 kPa with (right panel) and without (left panel) modulation by respiratory unloading. In this cat, tidal volume increased on average by 20% with unloading in spite of a marked down-regulation in the total number of impulses in the phrenic nerve bursts. Simultaneously, the respiratory rate increased on average by 15%. This increase in minute ventilation normalized the arterial PCO₂ level. AU: arbitrary units.](image)
were no statistically significant differences between the pre- and post-unloading baseline values of any of the target variables (Table 1). We assume that the control of breathing system was left intact in our cats, as there were no major hypoxaemic events that could have disturbed this function. Also, the type of anaesthesia used in our study does not interfere in any major way with the regulation of spontaneous breathing (15). An intact control of breathing system was an essential prerequisite for the efficacy of respiratory mechanical unloading in this study, as no other modality of mechanical ventilatory support was provided as backup.

Effects of respiratory unloading on ventilation and phrenic nerve activity

During unloading, the subject initiates each and every breath and controls the extent and timing of those breaths. The respirator follows and amplifies the effect of the subject’s respiratory muscle activity on ventilation. In our study, the increase in tidal volume and the decrease in PaCO2 reflect this enhancement during unloading. Nevertheless, respiratory mechanical unloading did have a small, though significant, modifying effect on the output pattern of the respiratory centre, in that the spontaneous respiratory rate increased slightly but consistently, while the total number of impulses in the phrenic nerve burst was down-regulated. As the inspiratory time remained unchanged, the mean impulse frequency in the phrenic nerve bursts decreased with unloading. The latter is regarded as an index of central respiratory drive (19, 20). Thus, there was a slight decrease in central respiratory output in response to respiratory mechanical unloading. However, the effect of respiratory unloading on ventilation far exceeded the slight decline in phrenic nerve activity. We observed a similar response pattern in previous experiments on animals with much less severe or no lung injury (8, 18). The present study extends these findings to a model of severe pulmonary parenchymal injury with acidosis and hypercapnia. Our results cannot determine whether this slight decline in central respiratory output during unloading is directly related to the lower arterial PCO2 levels, or to the higher pH levels, or possibly to an increased afferent inhibitory input from pulmonary stretch receptors.

Effects of respiratory unloading on arterial oxygenation

Arterial oxygenation did not improve significantly with unloading. There was a tendency, however, to higher PaO2 levels and the power of the study may have been too small to corroborate this statistically. The large venous admixture in this animal model is probably related to a low functional residual capacity. We have previously shown that the functional residual capacity depends on the end-expiratory pressure applied during unloading (9). The absence of a strong effect on oxygenation may therefore be related to the fact that we kept the same end-expiratory pressure level during unloading and during CPAP. In the present study, full-cycle resistive unloading was used. This lowers ventilator pressure during expiration compared to the use of resistive unloading during inspiration only. It leads to a lower mean airway pressure and may, therefore, have contributed to the lack of improvement in oxygenation in this model of severe surfactant deficiency.

Gain settings for respiratory mechanical unloading

We have chosen a uniform gain of 2.0 kPa/l/s for the resistive part of unloading across all studies. We did not expect the airway resistance to be much elevated in the cats, as the lavage procedure primarily deprives the lung of surfactant, thereby reducing alveolar compliance while leaving the resistance largely unaffected. Thus, this degree of resistive unloading was appropriate to compensate just for the resistance of the cats’ 3.0 mm inner diameter endotracheal tubes, and possibly some part of the airway resistance. Our gain settings for elastic unloading varied more between cats, as the reduction in alveolar compliance with the lavage procedure differed between animals. With a mean gain of 0.0299 kPa/ml and a mean tidal volume of 34.3 ml, we applied on average an end-inspiratory airway pressure of 1.53 kPa (0.5 kPa of PEEP plus the product of tidal volume and ventilator elastance gain). This is a fairly low airway pressure cost of ventilation during unloading considering the severity of the pulmonary function derangement in our cats.

Limitations of the study

The present study is preliminary with respect to a variety of aspects that await evaluation. The design of this study does not prove superiority of respiratory mechanical unloading in comparison with other modes of assisted positive pressure ventilation, particularly newer modalities such as pressure support or pressure regulated volume support. To further substantiate our results, a more prolonged use of respiratory unloading appears necessary in a future trial with subjects being exposed to respiratory unloading in comparison with controls undergoing conventional ventilation only. Data of the present study have limited validity for an application of respiratory unloading in newborns, and especially premature infants with an immature respiratory control centre. Unlike adult animals, they exhibit periodic breathing with alternating periods of hypopnea, bursts of hyperventilation when handled or agitated, apnoeas. The positive feedback system that is inherent to the technology of respiratory mechanical unloading (10) may accentuate these extremes leading to larger fluctuations in PaCO2 and tidal volumes unless limits are imposed on the delivered ventilator pressure and a backup conventional mechanical ventilation is provided.
during apnoeic episodes. Moreover, newborns, unlike the investigated animal model, invariably have some leakage around the uncuffed endotracheal tube. Such leak will be interpreted by the unloading device as inspiratory effort and result in an additional increase in ventilator pressure which would be out of proportion. Therefore, an infant ventilator in the unloading mode must employ algorithms that allow the device to recognize an endotracheal tube leak and to adjust the delivered ventilator pressure waveform accordingly.

In conclusion, respiratory mechanical unloading appears to be an effective means of overcoming the mechanical constraints placed on ventilation during spontaneous breathing by a compromised lung parenchyma. Under the circumstances of the study, unloading in these cats enabled their largely intact central respiratory controller to turn a state of severe hypoventilation into normoventilation and subsequently maintain a steady state. Thus, unloading was effectively used in this study as a mode of assisted mechanical ventilation that employed spontaneous respiratory activity to normalize ventilation in subjects with severely injured lungs. We therefore speculate that this technique may avoid the problem of ‘fighting the ventilator’ and contribute to a reduction in barotrauma and the use of sedatives in small subjects undergoing assisted ventilation for respiratory failure due to severe pulmonary parenchymal damage.

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References

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