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Mild hypothermia reduces ventilator induced lung injury, irrespective of reducing respiratory rate

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Abstract

In the era of lung–protective mechanical ventilation using limited tidal volumes, higher respiratory rates are applied to maintain adequate minute volume ventilation. However, higher respiratory rates may contribute to ventilator induced lung injury (VILI). Induced hypothermia reduces carbon dioxide production and may allow for lower respiratory rates during mechanical ventilation. We hypothesized that hypothermia protects from VILI and investigated whether reducing respiratory rates further enhance lung protection in an *in vivo* model of VILI. During four hours of mechanical ventilation, VILI was induced by tidal volumes of 18 ml/kg in rats, with respiratory rates set at 15 or 10 breaths/minute in combination with hypothermia (32°C) or normothermia (37°C). Hypothermia was induced by external cooling. A physiological model was established. VILI was characterized by increased pulmonary neutrophil influx, protein leak, wet weights, histopathology score and cytokine levels compared to lung protective mechanical ventilation. Hypothermia decreased neutrophil influx, pulmonary and systemic interleukin–6 levels, histopathology score and tended to decrease pulmonary protein leak. Reducing respiratory rate in combination with hypothermia did not further reduce parameters of lung injury. In conclusion, hypothermia protected from lung injury in a physiological VILI model by reducing inflammation. Mild lowering of the respiratory rate did not further enhance protection.

Introduction

Mechanical ventilation can initiate as well as exacerbate lung injury, referred to as ventilator induced lung injury (VILI) thereby worsening other organ functions and contributing to mortality (1). The mechanisms of VILI involve mechanical processes, including overstretching and repetitive opening and closing of alveoli (2). Also, a pro–inflammatory state is apparent, including cytokine production (3) influx of neutrophils (4) and a procoagulant state (5). It is thought that these processes interact.

The use of limited tidal volumes of 6 ml/kg reduces morbidity and mortality in patients with acute lung injury (ALI) (6;7). This "protective" mechanical ventilation strategy is adopted in guidelines worldwide (8). To maintain adequate minute volume ventilation during lung protective ventilation, higher respiratory rates are applied, which may amplify lung injury by repetitive alveolar collapse (9). In an experimental model, lower respiratory rates was shown to protect against VILI (10). However, use of low respiratory rates combined with low tidal volume ventilation is limited by development of respiratory acidosis. Although (mild) respiratory acidosis may be protective in ALI (11;12), severe acidosis is usually avoided, because of detrimental effects on immune function (13), right ventricular function (14) and oxygenation (15). New strategies are warranted, as is emphasized by recent reports on management of ICU patients, in which ventilation with deviated tidal volumes of 8–9 ml/kg was applied because of hypoxemia and acidosis (16).

Induced hypothermia is applied in the intensive care patient to ameliorate hypoxia–induced brain damage following a cardiac arrest (17). Also, hypothermia was found to be protective in several models of lung injury, including VILI (18–20). Besides a reduction in inflammation, induced hypothermia reduces metabolism and thereby carbon dioxide production, which may allow for a lower respiratory rate to maintain adequate minute ventilation. In a VILI model, reducing respiratory rates in conjunction with hypothermia indeed augmented protection (21). However, the presence of severe alkalosis, occurring already after one hour of mechanical ventilation, hampers extrapolation of these results.

In the present study, we examined the effect of mild hypothermia in a model of VILI with a normal acid–base balance. We hypothesized that applying lower respiratory rates during hypothermia further reduces lung injury. Results may contribute to the question whether we should target the inflammatory response or minute volume ventilation in future studies of VILI.

Methods

The study was approved by the animal care and use committee of the Academical Medical Centre, Amsterdam, the Netherlands. Animal procedures were carried out in compliance with Institutional Standards for Humane Care and Use of Animal Laboratory Animals.

Anesthesia and instrumentation

The experimental protocol is as described earlier (22). Male Sprague Dawley rats (n=8 per group, Harlan, The Hague, The Netherlands) weighing 350–400 g received an intraperitoneal injection of anesthesia mix (0.15 ml $100g^{-1}$ body weight) containing 90 mg kg^{-1} ketamine (Eurovet Animal Health B.V., Bladel, The Netherlands), 0.5 mg kg^{-1} medetomidine (Pfizer Animal Health B.V., Capelle a/d IJsel, the Netherlands) and 0.05 mg kg^{-1} atropine (Pharmachemie, Haarlem, the Netherlands). Anesthesia was maintained by infusion of 50 mg kg^{-1} ketamine at 0.5ml 100^{-1} hr^{-1} via the tail vein. Normal saline was administered at 2 ml $100g^{-1}hr^{-1}$. Tracheotomy was performed, after which a metal cannula was inserted in the trachea. The metal cannula was connected to a ventilator (Servo 300, Siemens, Sweden). Hemodynamic monitoring was done by inserting a polyethylene catheter into the carotid artery (Braun, Melsungen, Germany) which was connected to a monitor (Siemens SC900, Danvers, USA). Arterial blood gas analysis was performed hourly (Rapidlab 865 blood gas analyzer, Bayern, Mijdrecht, the Netherlands), uncorrected for body temperature (alphastat method), which is considered a safe approach in critical ill patients as corrected blood gases can lead to hypercapnia, cerebral vasodilatation and increased intracranial pressure (23). Rectal temperature was monitored continuously (ama–digit ad 15^{th}, Amarell, Kreuzwertheim, Germany).

Mechanical ventilation settings and induction of hypothermia

At baseline, all the animals were pressure controlled ventilated with 12 cmH_2O positive inspiratory pressure (PIP) and 5 cmH_2O positive end expiratory pressure (PEEP) with respiratory rate set at 35 breaths/min (lung protective (LP) mechanical ventilation). The PIP, PEEP and respiratory rate were changed to 23 cmH_2O, 0 cmH_2O and 15 breaths/min respectively in the VILI normal rate group and the respiratory rate was reduced to 10 breaths/min in the VILI low rate group without changing the PIP and PEEP levels. Tidal volumes were measured using a pneumotachometer (HSE, Harvard apparatus, Manheim, Germany) specific for rats. The pneumotachometer was calibrated using a 1 mL syringe according to the manufacturer's instruction. Tidal volumes were recorded using respiration software (HSE–BDAS basic data acquisition, Harvard apparatus, Manheim, Germany). The tidal volumes during LP mechanical ventilation were ~8.5 ml kg^{-1} and in both VILI groups, the tidal volumes were ~18 ml kg^{-1}. The inspired oxygen fraction was kept at 60 % and the

inspiration to expiration ratio at 1:2 in the experimental groups. Hypothermia was induced by placing icepacks on the abdomen, until rectal temperature reached 32°C in both VILI and LP group. In the normothermia VILI and LP groups, temperature was kept at 37°C with a heating pad.

Bronchoalveolar lavage and assays

After 4 hours of mechanical ventilation, blood was withdrawn from the carotid artery, followed by *en block* removal of the lungs. The right lung was ligated, followed by bronchoalveolar lavage (BAL) of the left lung (3 x 2 ml NaCl), of which 3–4 ml was retrieved. Cell counts were determined using a hematocytometer (Z2 Coulter Particle Counter, Beckman Coulter Corporation; Hialeah, Florida, USA) in BAL–fluids (BALF). Differential counts were done on cytospin preparations stained with Giemsa stain (Dade Behring AG, Dudingen, Switzerland). In BALF supernatant, protein levels (Oz Biosciences, Marseille, France), as well as interleukin (IL)–6, CINC3, tumor necrosis factor (TNF)–α and IL–10 (ELISA, R&D Systems; Abingdon, United Kingdom) were determined according to instructions from the manufacturers.

Histopathology

The right lung top was Hematoxylin–Eosin stained and analyzed by a pathologist who was blinded for group identity. Interstitial inflammation, endothelialitis, bronchitis, edema and pleuritis were scored on a scale of 0 – 4: 0 for normal lungs, 1 for <25% lung involvement, 2 for 25 – 50% involvement, 3 for 50−75% involvement and 4 for >75% lung involvement. Total histology score is the sum score of all parameters. The remaining right lobes were used to determine wet weight.

Statistical analysis

Data are presented as mean±SD in the table or as mean±SEM in the figures. Intergroup differences were analyzed by analysis of variance and Bonferroni's post–hoc test, or by a Kruskal–Wallis test with Mann−Whitney *U* test according to the data distribution. A p value of < 0.05 was considered significant. Statistical analyses were carried out using SPSS version 16 (SPSS inc., Illinois, USA).

Results

A physiological model of VILI

Mean arterial pressure decreased in the experimental groups over time, but did not differ between groups and never dropped below 65 mmHg (Figure 1A + B). Hypothermia resulted in a decreased heart rate. Arterial blood gases remained within physiological limits in all

groups (Table). Respiratory rates needed to be reduced in VILI groups, due to application of higher PIP (Table). Lowering the respiratory rate with 33% in the low rate group, did not result in acid–base disturbances (Table).

Table. Arterial blood gas analysis in a physiological rat model of lung protective (LP) and lung injurious mechanical ventilation.

	Time (hr)	LP		Ventilator induced lung injury			
				Normal rate		Low rate	
		37°C	32°C	37°C	32°C	37°C	32°C
pH	T = 0	7.47±0.05	7.49±0.05	7.49±0.04	7.45±0.06	7.47±0.07	7.46±0.06
	T = 1	7.46±0.05	7.48±0.06	7.53±0.06	7.57±0.08	7.41±0.02	7.41±0.06
	T = 2	7.44±0.07	7.46±0.07	7.45±0.05	7.49±0.05	7.38±0.04	7.39±0.06
	T = 3	7.41±0.08	7.41±0.05	7.40±0.07	7.41±0.05	7.40±0.03	7.34±0.04
	T = 4	7.40±0.09	7.43±0.06	7.36±0.05	7.38±0.05	7.35±0.06	7.40±0.04
pCO_2, kPa	T = 0	4.1±0.8	3.9±0.9	3.9±0.4	4.4±0.9	4.2±1.1	4.3±0.8
	T = 1	4.2±0.7	4.4±0.7	3.4±0.9	3.0±1.0	4.8±0.5	4.8±0.6
	T = 2	4.1±1.0	4.5±0.7	4.3±0.6	3.7±1.0	5.2±0.6	4.8±0.6
	T = 3	4.0±1.4	4.7±0.7	5.0±0.9	4.4±0.6	4.9±0.5	5.0±0.7
	T = 4	5.3±2.0	4.4±0.7	5.8±1.7	4.7±0.8	4.5±1.4	4.7±0.4
pO_2, kPa	T = 0	39±2	40±2	40±3.1	40±3	40±2	40±3
	T = 1	41±2	44±2	35±4	39±3	37±3	40±2
	T = 2	41±3	44±3	33±6	40±4	38±2	40±2
	T = 3	40±3	43±3	30±9	37±5	31±10	41±3
	T = 4	41±4	44±4	25±12*	34±8†	27±13*	38±4†
HCO_3, mmol/L	T = 0	22±3	22±3	22±2	22±3	22±2	22±1
	T = 1	22±2	24±4	21±2	19±4	22±2	22±2
	T = 2	20±3	23±1	22±2	20±4	23±2	21±2
	T = 3	18±3	22±2	22±2	20±4	22±1	21±2
	T = 4	24±11	22±3	21±3	20±3	18±4	21±3
Base excess	T = 0	-0.6±2.3	-0.5±1.2	-0.2±2.3	-0.9±2.3	-0.4±1.3	-1.2±1.4
	T = 1	-0.2±2.5	1.4±3.4	-0.3±1.3	-0.2±2.2	-2.0±1.6	-1.7±2.6
	T = 2	-2.7±3.0	-0.1±2.0	-1.0±2.3	-1.5±2.5	-2.2±1.4	-3.2±1.7
	T = 3	-5.0±2.3	-2.1±1.8	-1.9±2.2	-3.2±3.6	-2.8±0.9	-3.3±2.8
	T = 4	-0.5±10	-1.7±3.0	-4.9±2.9	-4.8±3.3	-6.7±2.8	-3.3±2.8
Respiratory rate, breath/min	T = 0	35±0	35±0	35±0	35±0	35±0	35±0
	T = 1	34±3	31±4	19±2	21±5	11±1	10±2
	T = 2	34±2	31±4	15±0	16±2	11±1	10±2
	T = 3	34±2	31±4	15±0	15±0	11±2	10±2
	T = 4	33±4	31±4	15±0*	14±2	10±0‡	10±1#

Data shown as mean ± SD. *: VILI 37°C vs. LP 37°C, †: VILI 37°C vs. VILI 32°C normal rate, #: VILI 32°C low rate vs. VILI 32°C normal rate and ‡: VILI 37°C normal rate vs. VILI 37°C low rate, the symbols indicates: $p < 0.05$.

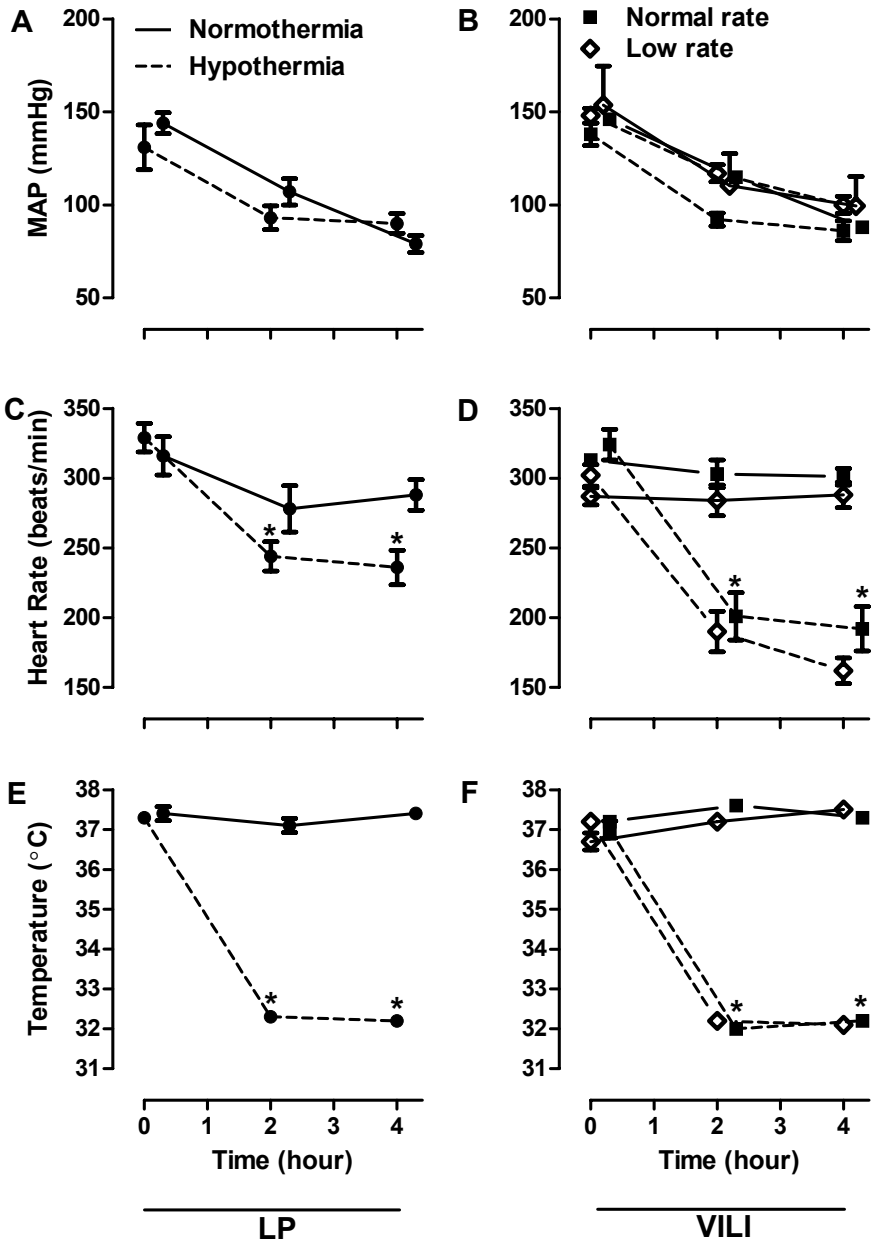

Figure 1: The effect of hypothermia on mean arterial pressure (MAP) (A+B), heart rate (C+D) and body temperature (E+F) during lung protective (LP) and lung injurious mechanical ventilation creating ventilator induced lung injury (VILI). Straight line and dotted lines represents normothermia and hypothermia respectively. The combination of straight line with closed squire and open diamond with dotted line represents VILI normothermia normal rate and VILI hypothermia low rate respectively. Closed square with dotted line represents VILI hypothermia normal rate (in B, D, and F). Mean ± SEM, *: vs. normothermia control, $p<0.05$.

Local and systemic inflammation in VILI

VILI was associated with an increase in levels of protein in the BALF and lung wet weight (Figure 2) compared to LP ventilation ($p<0.05$ for all), indicating pulmonary leakage. There was an influx of neutrophils to the lung (Figure 2C,) and pulmonary levels of IL–6 were increased (Figure 3A, $p<0.05$ for all). Increase in inflammatory parameters in the lung was accompanied by an increase in lung histopathology score compared to LP ventilation (Figure 4 + 5, $p<0.05$). Injurious mechanical ventilation led to an increase in systemic levels of IL–6 (Figure 3B, $p<0.05$). IL–10, CINC3 and TNF–α were not detectable in plasma or BALF. Increased inflammation in VILI was accompanied by a reduction in arterial pO_2 compared to LP ventilated groups (Table, $p<0.05$).

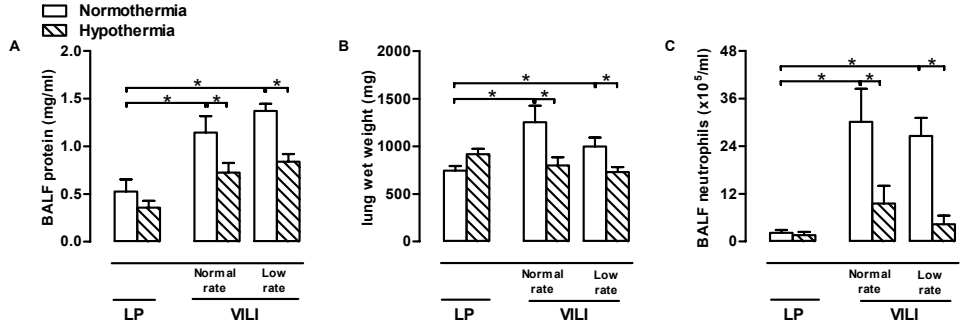

Figure 2: The effect of hypothermia on levels of total protein (A), wet weight (B) and neutrophil influx (C) in bronchoalveolar lavage fluid (BALF) during lung protective (LP) mechanical ventilation and lung injurious ventilation creating ventilator induced lung injury (VILI). Mean ± SEM, *:p<0.05.

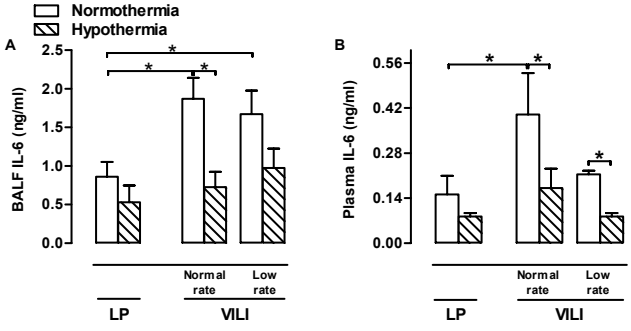

Figure 3: The effect of hypothermia on levels of IL–6 in bronchoalveolar lavage fluid (BALF) (A) and plasma (B) during lung protective (LP) mechanical ventilation and lung injurious ventilation creating ventilator induced lung injury (VILI). Mean ± SEM, *: p<0.05.

The effect of hypothermia on pulmonary inflammation in VILI

Hypothermia reversed the rise in pulmonary inflammatory parameters induced by the ventilator in both VILI groups compared to normothermic controls, including lung wet weight, pulmonary neutrophil influx, IL–6 concentrations and lung histopathology score (Figure 2, 3, 4 + 5 $p<0.05$ for all). Hypothermia tended to reduce protein concentration in BALF. Also, hypothermia prevented a decrease in arterial pO_2 (Table, $p<0.05$).

The effect of lower respiratory rates against VILI

Reducing respiratory rate in combination with hypothermia did not enhance the protective effect of hypothermia on parameters of pulmonary inflammation (Figure 2+3), nor on oxygenation (Table) in VILI. Also, reducing respiratory rate during normothermia had no effect on oxygenation and pulmonary and systemic inflammatory parameters in VILI.

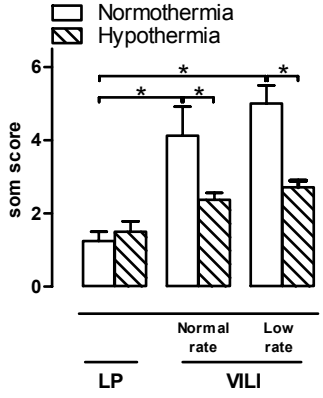

Figure 4: The effect of hypothermia on histopathology score of animals during lung protective (LP) mechanical ventilation and lung injurious ventilation creating ventilator induced lung injury (VILI) with in the VILI groups the respiratory rate set at 15 breaths/min (normal rate) or 10 breaths/min (low rate). Mean ± SEM. *:$p<0.05$.

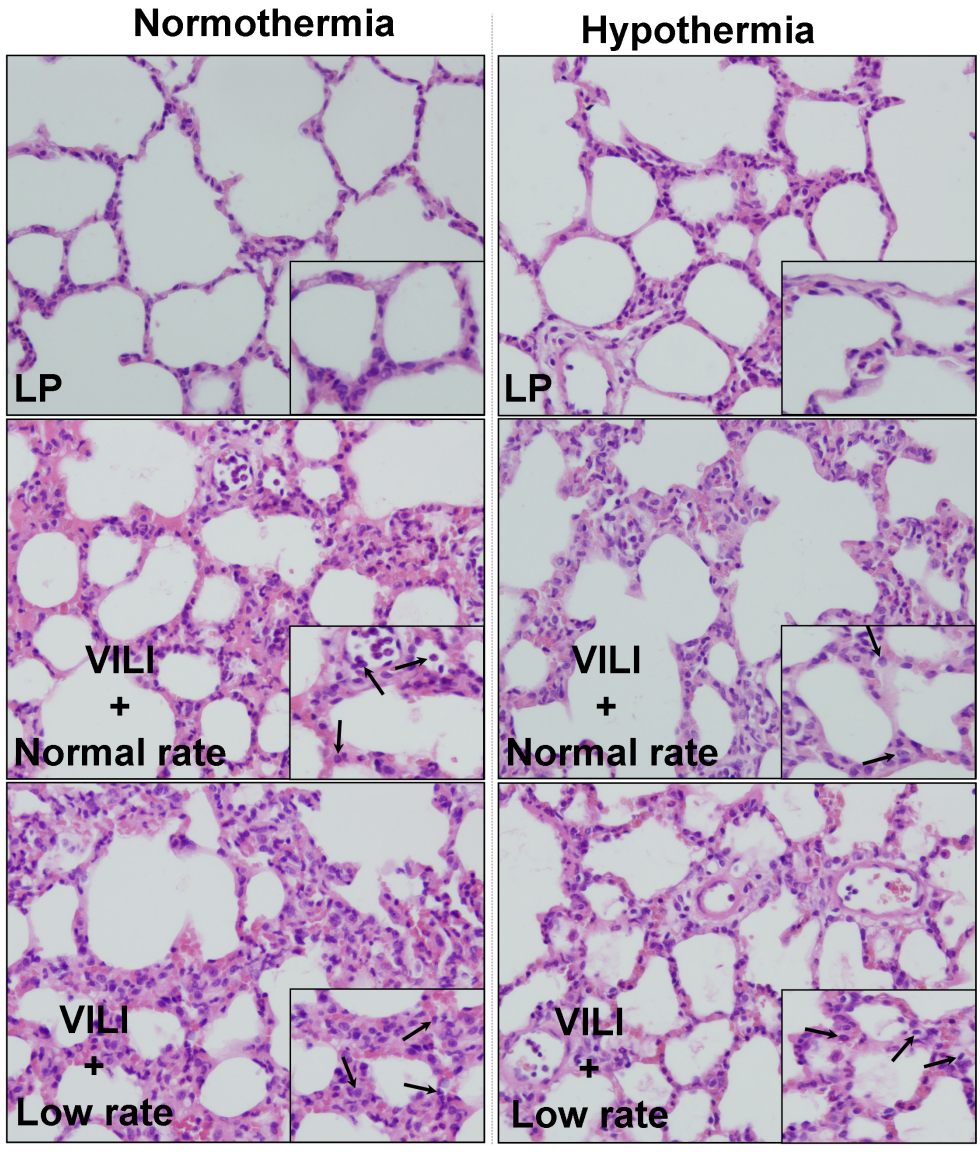

Figure 5: Representative Hematoxylin and Eosin photographs of the lung sections (magnification 20x) of animals during lung protective (LP) mechanical ventilation or lung injurious ventilation creating ventilator induced lung injury (VILI) with body temperature kept at 37°C (normothermia) or 32°C (hypothermia). Arrow: neutrophils.

Discussion

In an *in vivo* VILI model with normal acid–base balance, hypothermia reduced lung inflammation caused by the mechanical ventilator. Application of lower respiratory rates did not enhance the protective effect of hypothermia on lung injury.

The present study describes a physiological model of VILI. In previous VILI models, ventilation with large tidal volumes (3;18) resulted in severe alkalosis (19;21) or shock with acidosis (18), limiting the time of mechanical ventilation in the experiments to less than 2 hours (24;25). As pH status affects endpoints of VILI (26;27), extrapolation of results of experimental studies investigating the effect of hypothermia in VILI is hampered. In our model, arterial blood gas analysis remained within physiological limits, also after 4 hours of mechanical ventilation.

High positive inspiratory pressure caused alveolar–endothelial membrane disruption, with leakage of large proteins leading to permeability edema and gas exchange disturbances, in line with previous reports (18;19). Induction of hypothermia reduced permeability edema and improved oxygenation, demonstrated by lower pulmonary protein concentration, lower wet weight and higher arterial pO_2 respectively, with a concomitant decrease in pro–inflammatory mediators. In line with this, hypothermia reduced neutrophil influx into the lung in our model (19;20), together with a decrease in IL–6 levels in BALF. Other cytokine levels were not increased in VILI. This is in line with some reports (28;29) but not with all (20;21). There are several explanations for discrepant results. We used relatively low positive inspiratory pressures to create lung injury, in contrast to some previous models (3;4;18), as well an *in vivo* design. Also, difference in duration of VILI as well in duration of hypothermia may contribute to differential results. An elevation of pulmonary levels of TNF–α early in the course of inflammation may have returned to low levels at the end of the experiment (20). A short course of hypothermia may be more effective in reducing pro–inflammatory cytokine levels (19) and to achieve a favorable change in the balance between pro– and anti–inflammatory cytokines by induction of IL–10 (30) than extended courses of hypothermia (29). In addition, the depth of hypothermia may account for differences in outcome. Whereas mild hypothermia is protective in ALI, deep hypothermia has been found to worsen lung injury (30–32).

Mechanical ventilation can also perpetuate systemic inflammation (33;34). High plasma cytokines associated with mechanical ventilation was found to contribute to multiple organ failure (33). Of note, the protective effect of mechanical ventilation with low tidal volumes (7) was associated with lower systemic IL–6 levels compared to the application of conventional tidal volumes.

In the era of lung protective mechanical ventilation, higher respiratory rates are applied to meet adequate minute volume for ventilation (7). However, repetitive opening and closing of alveoli may be one of the mechanisms of VILI. Indeed, in vitro, high respiratory rates were found to induce injury to alveolar cells (35). The combination of high respiratory rates with high tidal volumes aggravates lung injury (35–37). Thereby, reducing respiratory rates may enhance lung protection. In this study, a mild reduction in respiratory rate did not further enhance hypothermia–mediated protection, nor did it alter markers of VILI during normothermia. Although a larger reduction in respiratory rate was previously found to offer protection (21;37), gross abnormalities in acid base balance or an *ex vivo* setting in these models hamper clinical applicability. We provide the first *in vivo* data, which do not support interventions targeted at reducing respiratory rates in mechanically ventilated patients. However, a limitation of our findings is that the reduction in respiratory rate was only mild. This does not exclude that a larger reduction in respiratory rate may be advantageous. As pointed out, the development of severe acid–base imbalances is a limitation to such applications. Also, we used healthy animals rather than animals with pre–existing lung injury.

Conclusion

Hypothermia protected from lung injury in a physiological VILI model. Mildly lowering the respiratory rates did not further enhance lung protection. Whether high respiratory rates can be applied safely in patients with lung injury, cannot be dissected from our results. Targeting inflammation however, is a promising approach to reduce lung injury in mechanically ventilated patients.

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