Intensive Care Med (2000) 26: 1664–1669
DOI 10.1007/s001340000664

EXPERIMENTAL

M. Nishimura
O. Honda
N. Tomiyama
T. Johkoh
K. Kagawa
T. Nishida

Body position does not influence the location of ventilator-induced lung injury

Received: 3 January 2000
Final revision received: 1 August 2000
Accepted: 3 August 2000
Published online: 14 October 2000

M. Nishimura (✉)
Intensive Care Unit,
Osaka University Hospital,
2-15 Yamadaoka, Suita,
Osaka 565–0871, Japan
E-mail: masaji@hp-icu.med.osaka-u.ac.jp
Phone: +81-6-6879 5811
Fax: +81-6-6879 5823

O. Honda · N. Tomiyama · T. Johkoh
Department of Radiology,
Osaka University Medical School,
1-1 Yamadaoka, Suita,
Osaka 565-0871, Japan

K. Kagawa
Department of Anesthesiology,
National Cardiovascular Center,
5-7-1 Fujishiro-dai, Suita City,
Osaka 565-0873, Japan

T. Nishida
Department of Anesthesia,
Nakatsu-Saiseikai Hospital,
2-10-39 Shibata, Kita-ku,
Osaka 530-0012, Japan

Abstract *Objective*: To ascertain whether the locations of ventilator-induced lung injury (VILI) are influenced by body position.
Design: Randomized prospective short-term study.
Setting: Animal laboratory at a university school of medicine.
Interventions: Twelve white rabbits were mechanically ventilated in IMV mode with an infant ventilator (V.I.P. Bird, Bird Products, Palm Springs, Calif., USA). Based on the results of a preliminary study to determine the ventilator settings at which the lungs of rabbits were injured within 5 h in the supine position, the ventilator was set at F_IO_2 0.21, at a rate of 30/min, T_I 0.6 s, peak inspiratory pressure 30 cm H_2O, inspiratory flow 10 l/min with no applied positive end-expiratory pressure (PEEP). Six of the animals were tested in the supine position and the other six in the prone position. Respiratory gases were measured and CT scanning was performed every 30 min. The animals were ventilated for 5 h or until pulmonary parenchymal opacification was detected. The lungs were divided into three areas from apex to base and three levels from ventral to dorsal, and the location of opacification was ascribed according to this scheme. After the experiment, the lungs were excised and examined histologically.
Measurements and results: Parenchymal opacification occurred mainly in the dorsal lung areas. The time from the beginning of ventilation to the appearance of lung damage was 60–120 min in the supine (S) group, and 60–270 min in the prone (P) group, and it was significantly longer in the prone group ($P < 0.01$). We observed diffuse lung damage, including hyaline membrane formation, intra-alveolar edema, and infiltration of inflammatory cells.
Conclusions: Body position affected the time course of the development of VILI, but it did not affect the location.

Key words Mechanical ventilation · Lung injury · Body position

Introduction

Despite advances in critical care technology and increased knowledge about the syndrome, mortality in acute respiratory distress syndrome (ARDS) remains high. One of the reasons for high mortality is thought to be additional damage induced by mechanical ventilation itself [1, 2]. Even though measures are taken to protect the lungs when ventilating ARDS patients, mortality remains high [3]. Placing the patient in a prone position has been proposed as a relatively simple maneuver to improve oxygenation [4]. Experimental animal studies have suggested that the prone position causes less lung injury than the supine position owing to positive pressure ventilation [5]. In ARDS, the most severe form of acute lung injury (ALI), reports state that prone

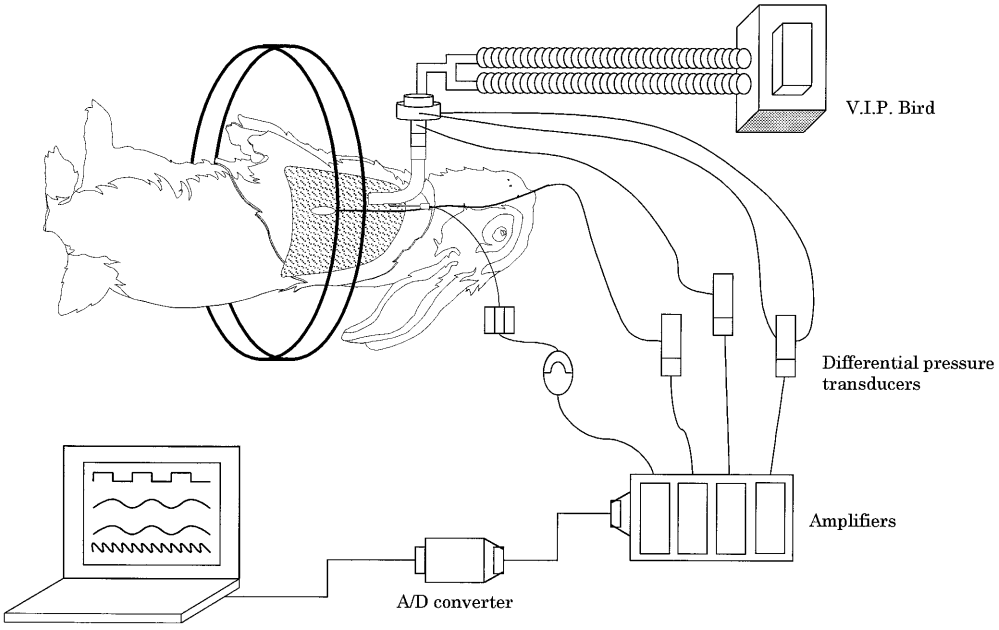

Fig. 1 Experimental setup of the study. The animals were ventilated with an infant ventilator in supine or prone position at the radiology laboratory. Chest CT was obtained every 30 min

placement results in decreased venous admixture and more uniform regional lung inflation. Few reports have shown, however, how different placement of the body may affect ventilator-induced lung injury (VILI).

The lung-protective approach involves keeping the lungs open throughout the respiratory cycle without injuring them. To protect the lungs from positive pressure ventilation, tidal volume (V_T) is limited and hypercapnia is permitted. Many patients can tolerate higher-than-normal CO_2 levels and are not severely affected by side effects due to hypercapnia. On the other hand, hypercapnia should be avoided if patients have intracranial hypertension. Although the adverse effects of hypercapnia on hemodynamics are reportedly transient [6], hypercapnia does increase pulmonary vascular resistance and worsens pulmonary hypertension in ARDS [7]. If the prone position is less traumatic for the lungs, the effects of hypercapnia will be less intense. In this study, to determine if body position affects the location of injury or the time course for its development, we administered positive pressure ventilation to two groups of healthy white rabbits placed either in the prone or the supine position and performed CT scans of the lungs at regular intervals.

Methods and materials

The study was approved by the Institutional Review Board at the Osaka University Medical School, and all animals were handled in accordance with National Institute of Health guidelines.

To determine appropriate ventilator settings for this study, we performed a preliminary experiment on 15 rabbits. The animals were anesthetized via an ear vein with an injection of 60–65 mg pentobarbital. They were set in a supine position (see Fig. 1). Local anesthesia (1 % lidocaine 2 ml) was infiltrated around the mid-neck. A tracheostomy was performed and a 4 mm ID endotracheal tube (Blue Line tracheostomy tube, SIMS Portex, Kent, UK) was inserted into the trachea. The internal carotid artery was cannulated with a 20-gauge catheter (Angiocath 20, Becton Dickinson Vascular Access, Sandy, Utah, USA) to monitor arterial pressure (Custom Product, Abbott Ireland, Sligo, Republic of Ireland) and to aspirate blood for respiratory gas measurements. Respiratory gases were measured (ABL-3, Radiometer, Copenhagen, Denmark) every 30 min after the start of mechanical ventilation. The animals were connected to a ventilator (V.I.P. Bird, Bird Products, Palm Springs, Calif., USA) through a standard ventilator circuit. Rectal temperature was monitored (Mon-a-therm/Model 6500, Mallinckrodt, St. Louis, Mo., USA) and it was maintained within the range of 40 ± 1 °C using an electric blanket. They were set in a supine position, and sedated and paralyzed with continuous infusion of sodium pentobarbital (5–10 mg kg^{-1} h^{-1}) and pancuronium bromide (0.1–0.2 mg kg^{-1} h^{-1}). Crystalloid solution was infused 7–10 ml kg^{-1} h^{-1}. During the course of the experiment, this infusion rate and the anesthetics dosages were adjusted to maintain arterial blood pressure within ± 10 % of that of the beginning of the experiment.

To assess the effect of peak inspiratory pressure (PIP), PEEP, and F_IO_2, the rabbits were divided into three groups of five each. For the first group, the ventilator was set at F_IO_2 0.21, and PIP 30 cm H_2O; for the second group, the ventilator was set at F_IO_2 0.5, and PIP was lowered to 20 cm H_2O; for the third group, the ventilator was set at F_IO_2 0.5, peak inspiratory pressure PIP 30 cm H_2O, and PEEP was applied at 5 cm H_2O. All animals were ventilated for 5 h or until the PaO_2 went below half of the initial value. PaO_2 went below one half of the initial value only in the first group, that is, animals ventilated in PIP 30 cm H_2O without PEEP; this occurred in two animals within 3 h, another within 4 h, and another within 5 h. At other ventilator settings, PaO_2 did not change significantly for at least 5 h of mechanical ventilation. Based on this finding, the ventilator was set at F_IO_2 0.21, at a rate of 30/min, T_I 0.6 s, PIP 30 cm H_2O, inspiratory flow 10 l/min with no applied PEEP.

An esophageal balloon (SmartCath Esophageal Balloon, Neonatal Catheter (5 Fr.), Bicore Monitoring Systems, Irvine, Calif.) was inserted through a nostril. The balloons were positioned where the largest cardiac oscillation was detected. It was attached to a pressure transducer (TP 603T, ± 50 cm H_2O, Nihon Kohden, Tokyo, Japan) to measure esophageal pressure. The signals were fed to an amplifier (AR-601G, Nihon Kohden, Tokyo, Japan). Airflow was measured at the airway openings of the tubes using a pneumotachometer (Hans Rudolph, Kansas City, Mo., USA) connected to a differential pressure transducer (TP-602T, ± 5 cm H_2O, Nihon Kohden, Tokyo, Japan), the signals from which were amplified (AR-601G, Nihon Kohden, Tokyo, Japan). Tidal volume (V_T) was calculated by digital integration of flow signals during the initial period of the experiment; the flow sensor was then removed because of the dead space it introduced. Five breaths were measured for V_T presentation. All signals were recorded in an IBM-compatible computer system using data acquisition software (WinDaq, Dataq Instruments, Akron, Ohio, USA) via an analog–digital converter (DI-220, Dataq Instruments, Akron, Ohio, USA). Subsequent data analysis was performed with dedicated software (WinDaq playback, Dataq Instruments, Akron, Ohio, USA).

Experimental protocol

Each animal was transported to the radiology laboratory after all the surgical procedures were performed. During transportation, the animals breathed spontaneously. Each animal received time-cycled, constant-flow mechanical ventilation at F_IO_2 0.21, at a rate of 30/min, T_I 0.6 s, PIP 30 cm H_2O, inspiratory flow 10 l/min with no applied PEEP. They were sedated and paralyzed in the same way as in the preliminary study. Six animals were placed in a supine position (S group; body weight 2522 ± 345 g) and the other six animals in the prone position (P group; body weight 2744 ± 208 g). Animals from both groups were ventilated for 5 h or until the parenchymal opacifications were detected on chest CT. After completion of the ventilation period, each animal was killed with an intravenous injection of sodium pentobarbital 400 mg.

CT scanning was carried out every 30 min after the start of mechanical ventilation. Scans, from apex to the base of the lungs, were obtained both at the end-expiratory phase and at the inspiratory phase. Thin-section CT images of all rabbits were obtained. All CT scans were performed with a HiSpeed Advantage scanner (General Electric Medical Systems, Milwaukee, Wis., USA). Whole lung CT scans were obtained at 7-mm intervals using 1-mm collimation. The field of view was 10–12 cm with a 512 × 512 matrix and all images were reconstructed with a high-spatial frequency algorithm. Technical factors for each scan were 120 kVp and 100 mAs. Images were viewed at window levels appropriate for pulmonary parenchyma (window width, 1200H; window level –700H).

To ascribe injury to specific areas, the lungs were conceived as comprising three levels: upper, the area above the carina; middle, at the side of the carina; lower, below the carina. Detection of parenchymal opacification in these three levels was discerned by radiologists. Each scan took about 5 s. When the animals were ventilated with the settings described above, transpulmonary pressure (the difference between the airway pressure and esophageal pressure) was around 25 cm H_2O. For the scanning of inflated lungs, inflation had to be maintained for 5 s, during which 25 cm H_2O of inflation pressure was applied to match the transpulmonary pressure. Upon completion of the experiment, the lungs were excised and examined histologically.

Table 1 Time and locations of occurrence of parenchymal opacification in the lungs during high positive pressure ventilation in supine and prone rabbits (*S* supine, *P* prone, *R/L* right/left lung, *U/M/L* upper/middle/lower level, *D/H/V* dorsal/hilar/ventral region)

Position	Time (min)	Site of injury		
		R/L	U/M/L	D/H/V
S	120	R/L	L	D
S	60	R/L	L	D
S	60	R/L	L	D
S	90	R/L	L	D
S	90	R/L	L	D
S	60	L	L	V
P	60	R	L	D
P	180	R/L	L	V
P	90	R/L	L	D
P	270	L	L	D
P	150	L	L	D
P	120	L	L	D

Statistical analysis

Analysis of variance was used to compare the respiratory data of animals in the two groups. To compare the appearance of parenchymal opacification between supine and prone, we performed the Kruskal-Wallis test. To compare the incidence of parenchymal opacification among locations, we performed the Friedman test. Bonferroni's adjustment for post hoc tests was used when comparing data from different locations. The time elapsed from the beginning of mechanical ventilation and appearance of opacification between the groups was compared by Mann Whitney U test. Significance was defined as $P < 0.05$ and the limit of confidence interval of the true mean was set at 95 %.

Results

Parenchymal opacification was detected in all animals within 5 h. The incidence of this type of damage was not significantly different between the S and P groups. CT scans showed damage in the lower areas of the lungs more often than in the other areas (in both the S and the P group, $P < 0.01$). No abnormal findings were detected in the upper and middle levels of the lungs in either group. Comparing the ventral and dorsal regions, in both groups, the dorsal lungs, which were mainly affected by high positive pressure ventilation, were injured in five out of six animals. Only one animal in each group showed parenchymal opacification in the ventral zone of the lungs. Figures 2 and 3 show representative CT scans of the chests of animals from each group obtained at (Fig. 2) 30 min after the beginning of mechanical ventilation and (Fig. 3) at the time parenchymal opacifications were detected.

Table 1 shows the site of VILI detected on chest CT scans for each animal. The V_Ts of the S group were 78.8 ± 3.3 ml and V_Ts for the P group were 79.8 ± 8.2 ml. Transpulmonary pressure (Ptp) levels recorded

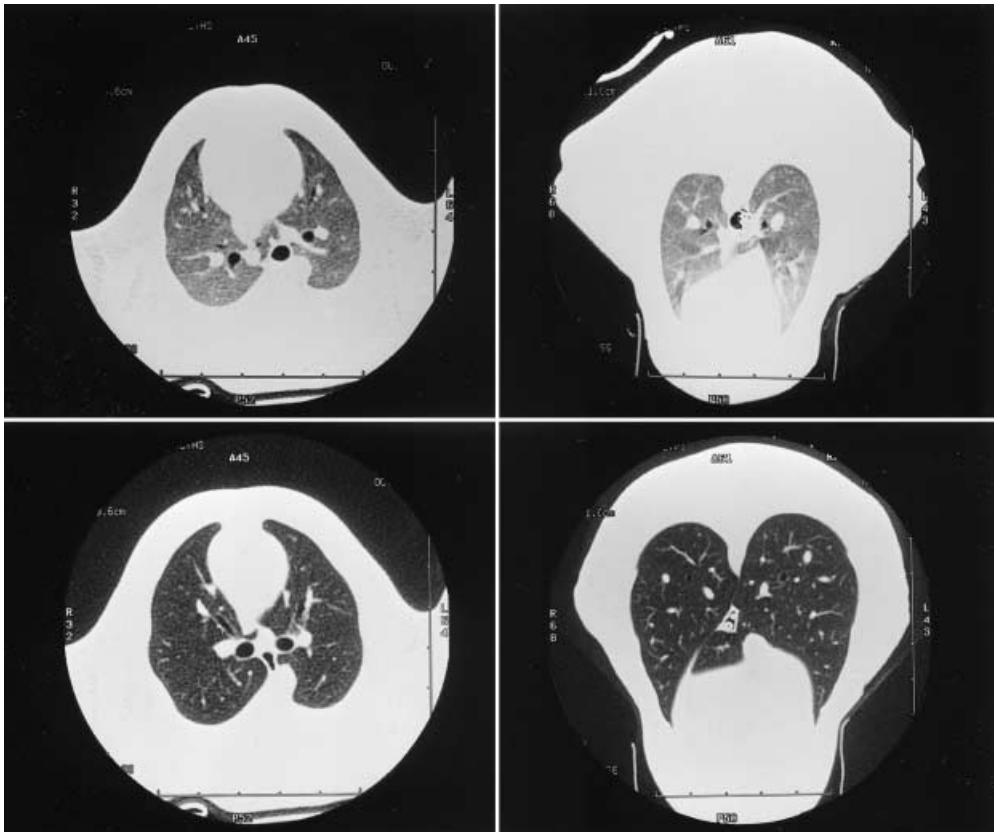

Fig. 2 Representative chest CTs of each group of animals. Upper panels show expiratory phase CT, and lower panels show inspiratory phase CT at 30 min after initiation of mechanical ventilation. Left column were CTs of the animal in the S group, and right column were CTs in the P group

for each group were: S, 24.05 ± 2.96 cm H_2O; P, 23.46 ± 3.31 cm H_2O.

The time elapsed from the beginning of mechanical ventilation to the appearance of parenchymal opacification in the lungs was 60–120 min in the S group (a median of 75 min), and 60–270 min in the P group (a median of 135 min). It was significantly longer in prone than in supine animals ($P < 0.01$). The value of PaO_2 just after the initiation of mechanical ventilation was not significantly different between the groups (119.7 ± 12.6 mmHg in the S group and 107.5 ± 12.4 mmHg in the P group). At the appearance of parenchymal opacification, PaO_2 did not differ significantly between the groups, either (116.9 ± 19.0 mmHg in the S group and 105.5 ± 14.5 mmHg in the P group).

Examination of the lungs revealed infiltration of inflammatory cells in lung tissue, hyaline membrane formation, epithelial destruction, interstitial and intra-alveolar edema, and intra-alveolar hemorrhage. The extent of these conditions corresponded to the exudative phase or the proliferative phase of diffuse alveolar damage.

Discussion

The major findings of this study are: (1) As detected by CT scanning of the chest, the positive pressure ventilation applied in this study injured the lungs of rabbits placed in a supine position; (2) similarly, animals in a prone position showed substantially the same type of VILI; (3) VILI was most in evidence in the lower areas of the lungs (4) in both the supine and prone positions, the dorsal area suffered more VILI than the ventral area.

High tidal ventilation indisputably induces severe lung damage, while evidence from numerous animal studies shows that high inspiratory pressure also induces severe lung injury [1, 2, 8]. Reducing tidal volume and permitting the ensuing hypercapnia has reduced the mortality of ARDS patients [9, 10, 11]. High tidal ventilation is also believed to injure the lungs of humans. Animal studies have reported injury to the entire lungs, but it has not generally been clear which parts of the lungs are worst affected by positive pressure ventilation. This study using CT scanning in a rabbit model, shows that VILI develops from the dorsal areas of the lungs and that the location of the injury is not related to body position. As far as the authors know, this is the first report to use CT scans to compare the location of lung injury related to supine and prone positions.

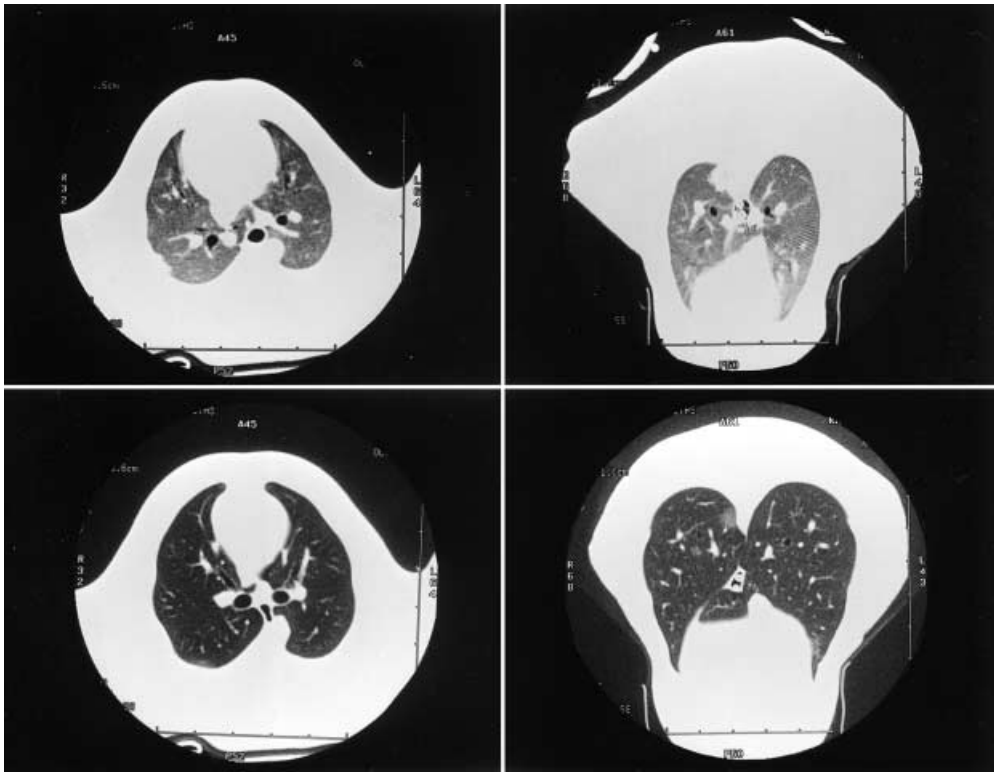

Fig. 3 Representative chest CTs of corresponding transverse slice in Fig. 2 at the time parenchymal opacifications were detected. Left column were CTs of the animal in the S group, and right column were CTs in the P group

Two mechanisms are thought to contribute to the development of VILI: overdistension of the alveoli; and shearing forces caused by the stress that occurs where collapsed areas of the lungs are reopened by positive pressure. High positive pressure ventilation with PIP as high as 30–45 cm H_2O induces diffuse alveolar damage. In this study, transpulmonary pressure was 24.1 ± 3.0 (S) and 23.5 ± 3.3 cm H_2O (P). Although the V_T values in this study, 31.8 ± 5.4 ml/kg supine and 29.4 ± 5.4 ml/kg prone, were less than reported by Dreyfuss [1, 2], V_T was high enough to induce lung injury from overdistension.

The forcible opening and closing of small airways and alveoli is repeated with every mechanical breath as the ventilation pressure swings below and above the lower inflection point (LIP); this may induce lung injury. In the present study, animals with normal lungs were ventilated mechanically, and no LIP was detected at the beginning of the study. Although the lungs of the animals might not have collapsed at end-expiration, the LIP indicates only the overall pressure–volume relationship of the entire lungs. It is well known that anesthesia is accompanied by increased venous admixture. Computed tomography provides good evidence of atelectasis in anesthetized patients. It is concentrated in the most dependent parts of both lungs and appears in almost 90% of patients who are anesthetized [12]. Collapse mostly occurs near the diaphragm in the supine position and lessens towards the apex. In the present study, CT scanning of the lungs was performed at both the expiratory and inspiratory phases. Images from the expiratory phase revealed that the density of the lungs was higher in the dependent areas regardless of body position (Fig. 3). This evidence suggests that collapse might occur during expiration in animals even when the lungs are normal. If this is so, forcible opening and closing of small airways and alveoli may play a part in lung injury.

Gravity is generally accepted as playing a major role in the distribution of ventilation and the regional expansion of the parenchyma of the lungs [13, 14]. Intrapleural pressure is lower at the top than at the bottom of the upright lung. The gradient of pleural pressure along the gravitational axis has been found to be gentler in prone than in supine pigs [14]. Consequently, in the prone position, pressures exerted regionally by the tidal volume may be distributed more evenly, thus making the small airways and alveoli in the dependent regions less subject to collapse. This means that, in the prone position, lower shearing forces are likely to occur at the small airways and alveoli in the dependent regions. For dogs, Broccard et al., have reported that the dorsal regions are more subject to VILI [5]. This injury may be due to shearing forces, and the dependent areas tended to be subject to positive pressure ventilation. Our results, using rabbits, do not accord with this finding. One of the most likely reasons is the difference in species.

The entire lungs of small animals are subject to positive pressure ventilation. In addition, gravity differences are less of a factor with small animals, which may not suffer the same kind of collapse of dependent areas during expiration that occurs in larger animals. Although the rabbits in the present study suffered VILI in both supine and prone positions, it took longer to notice parenchymal opacification of the lungs on CT images in the prone than in supine animals. The prone position may, therefore, offer some protection against VILI.

In the present study, the animals' lungs were ventilated with a relatively high V_T, and lung damage may have been induced by volutrauma. The sites of parenchymal opacification that were detected on CT scans were similar for both body positions, and the damage was due to overdistension rather than to shearing forces. The location of overdistension injury was not influenced by body position, so other anatomical factors may be more important. If the animal lungs had been ventilated with a smaller V_T, and if shearing forces play a major role in VILI, body position would have been more likely to influence the locations of lung injury.

Zakynthinos et al., have studied the effects of pressure support ventilation in ARDS patients, and report that, at least in the early phase of ARDS, pressure support ventilation improves intrapulmonary oxygenation [15]. They conclude that the improvement is probably due, at least in part, to alveolar recruitment augmented by active diaphragmatic contraction. Consequently, to restore spontaneous breathing (diaphragmatic contraction) it is important to protect the lungs both from collapse and from injury.

In conclusion, the development of VILI was not influenced by body position. The injury we found may have been due to high tidal volume that causes overdistension and in cases of this type of lung injury, at least in rabbits, anatomical factors may greatly contribute to VILI. For lung injury due to shearing forces, body position may affect the areas of injury.

Acknowledgements We thank Dr. Y. Fujino for his great help with the statistical analysis.

References

1. Dreyfuss D, Basset G, Soler P, Saumon G (1985) Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. Am Rev Respir Dis 132: 880–884
2. Dreyfuss D, Soler P, Basset G, Saumon G (1988) High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 137: 1159–1164
3. Roupie E, Lepage E, Wysocki M, Fagon J-Y, Chastre J, Dreyfuss D, Mentec H, Carlet J, Brun-Buisson C, Lemaire F, Brochard L (1999) Prevalence, etiologies, and outcome of the acute respiratory distress syndrome among hypoxemic ventilated patients. Intensive Care Med 25: 920–929
4. Lamm WJE, Graham MM, Albert RK (1994) Mechanism by which the prone position improves oxygenation in acute lung injury. Am J Respir Crit Care Med 150: 184–193
5. Broccard AF, Shapiro RS, Schmitz LL, Ravenscraft SA, Marini JJ (1997) Influence of prone position on the extent and distribution of lung injury in a high tidal volume oleic acid model of acute respiratory distress syndrome. Crit Care Med 25: 6–27
6. Carvalho CRR, Barbas CSV, Medeiros DM, Magaldi RB, Filho GL, Kairalla RA, Deheinzelin D, Munhoz C, Kaufmann M, Ferreira M, Takagaki TY, Amato MB (1997) Temporal hemodynamic effects of permissive hypercapnia associated with ideal PEEP in ARDS. Am J Respir Crit Care Med 156: 1458–1466
7. Puybasset L, Stewart T, Rouby J-J, Cluzel P, Mourgeon E, Belin M-F, Arthaurd M, Landault C, Viars P (1994) Inhaled nitric oxide reverses the increase in pulmonary vascular resistance induced by permissive hypercapnia in patients with acute respiratory distress syndrome. Anesthesiology 80: 1254–1267
8. Tsuno K, Prato P, Kolobow T (1990) Acute lung injury from mechanical ventilation at moderately high airway pressures. J Appl Physiol 69: 956–961
9. Hickling KG, Walsh J, Henderson S, Jackson R (1994) Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med 22: 1568–1578
10. Amato MBP, Barbas CSV, Medeiros DM, Magaldi RB, Schettino GPP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CRR (1998) Effect of protective ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338: 347–354
11. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342: 1301–1308
12. Tokics L, Strandberg A, Brismar B, Lundquist H, Hedenstierna G (1987) Computerized tomography of the chest and gas exchange measurements during ketamine anaesthesia. Acta Anaesthesiol Scand 31: 684–692
13. West JB, Matthews FL (1972) Stresses, strains, and surface pressures in the lung caused by its weight. J Appl Physiol 32: 332–345
14. Mutoh T, Guest RJ, Lamm WJE, Albert RK (1992) Prone position alters the effect of volume overload on regional pleural pressures and improves hypoxemia in pigs in vitro. Am Rev Respir Dis 146: 300–306
15. Zakynthinos SG, Vassilakopoulos T, Daniil Z, Zakynthinos E, Koutsoukos E, Katsouyianni K, Roussos C (1997) Pressure support ventilation in adult respiratory distress syndrome: short-term effects of a servocontrolled mode. J Crit Care 12: 161–172