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Effect of peak inspiratory flow on gas exchange, pulmonary mechanics, and lung histology in rabbits with injured lungs

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Abstract

Purpose. The aim of this study was to evaluate, using a rabbit model, the little-known effect of different levels of peak inspiratory flow on acutely injured lungs.

Methods. Fourteen male rabbits (body weight, 2711 ± 146 g) were anesthetized and their lungs were injured by alveolar overstretch with mechanical ventilation until Pa_{O_2} was reduced below 300 mmHg. Injured animals were randomly assigned to: the P group—to receive pressure-regulated volume-control ventilation (PRVCV; $n = 7$); and the V group—to receive volume-control ventilation (VCV; $n = 7$). Other ventilator settings were: fraction of inspired oxygen ($F_{I_{O_2}}$), 1.0; tidal volume, 20 ml·kg^{-1}; positive end-expiratory pressure (PEEP) 5 cmH_2O; and respiratory rate, 20 min^{-1}. The animals were thus ventilated for 4 h. Throughout the protocol, ventilatory parameters and blood gas were measured every 30 min. After the protocol, the lung wet-to-dry ratio and histological lung injury score were evaluated in the excised lungs.

Results. Throughout the protocol, peak inspiratory flow and mean inspiratory flow values in the P group were significantly higher than those in the V group (26.7 ± 5.0 l·min^{-1} vs 1.2 ± 0.2 l·min^{-1}, and 4.3 ± 0.3 l·min^{-1} vs 1.1 ± 0.1 l·min^{-1}; $P < 0.05$). The wet-to-dry ratio in the P group was also significantly higher than that in the V group (7.7 ± 0.9 vs 6.3 ± 0.5; $P < 0.05$). More animals in the P group than in the V group had end-of-protocol $Pa_{O_2}/F_{I_{O_2}}$ ratios below 200 mmHg (43% vs 0%; $P = 0.06$).

Conclusion. In rabbits with injured lungs, high peak inspiratory flow with high tidal volume (V_T) reduces the $Pa_{O_2}/F_{I_{O_2}}$ ratio and increases the lung wet-to-dry ratio.

Key words Peak inspiratory flow · Pressure-regulated volume-control ventilation · Volume-control ventilation · Wet-to-dry ratio · Ventilator-induced lung injury

Introduction

The mortality of acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is still high, and ventilator-associated lung injury (VALI) is believed to play a role in the poor outcome of patients with ALI/ARDS [1–5]. Low tidal volume (V_T) protects the lungs from VALI due to alveolar overdistension, and has been proven to improve the outcome of patients with ALI/ARDS [3–5]. To further decrease the mortality of ALI/ARDS, we have to avoid the harmful effects of mechanical ventilation as much as possible.

Recent studies have shown that high inspiratory flow damages the lungs. In a sheep model, Rich et al. [6] reported that reduction of inspiratory flow in animals with similar peak inspiratory pressure (50 cmH_2O) provided pulmonary protection. Maeda et al. [7] compared lung injuries in groups of normal rabbits ventilated at different inspiratory flows, but with the same V_T. Severe lung damage was found only in animals ventilated at the highest inspiratory peak flow. Both of these studies used large V_T to investigate the effect of inspiratory flow in animals with normal lungs. Meanwhile, Kotani et al. [8] found that mild overstretch at high inspiratory flow enhanced inflammatory signaling in perfused rabbit lungs. Dreyfuss et al. [9] reported that rat lungs injured with alfa-naphthyl thiourea were more susceptible to high-stretch lung injury than control lungs. This suggests that injured lungs are more vulnerable during mechanical ventilation than healthy lungs. However, in clinical practice, mechanical ventilation is commonly applied in patients with injured lungs.

In the present study, we tested the hypothesis that inspiratory flow would affect the development of ventilator-induced lung injury (VILI) in animal with injured lungs.

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Methods

This was a prospective, randomized laboratory animal investigation. We compared the effects of different inspiratory peak flow levels on damaged lungs. This study was conducted at the university laboratory, Department of Anesthesiology, Osaka University Medical School. The study was approved by the Laboratory Investigation Committee of Osaka University Medical School. Animals were cared for in accordance with the University's standards for the care and use of laboratory animals.

Male New Zealand white rabbits, whose weight ranged between 2500 g and 3000 g, were used in this study. Animals with Pa_{O_2} less than 450 mmHg at the first blood gas analysis were excluded.

Fourteen rabbits (body weight, 2711 ± 146 g) were anesthetized with an injection of 50–60 mg pentobarbital sodium (Abbott, North Chicago, IL, USA) via an ear vein and were set in a supine position on a heating pad. They received an infiltration of 1% lidocaine around the neck and were tracheostomized by the insertion of a 4-mm inner diameter endotracheal tube (Blue Line tracheostomy tube; SIMS Portex, Kent, UK). After this procedure, the animals were paralyzed with pancuronium bromide (Organon, Oss, The Netherlands) and were connected to a Servo 300 ventilator (Siemens-Elema, Solna, Sweden) with a standard ventilator circuit. Mechanical ventilation was started with the following settings: pressure control ventilation (PCV) level, 13 cmH_2O; fraction of inspired oxygen ($F_{I_{O_2}}$), 1.0; respiratory rate (f), 50 breaths·min^{-1}, with an inspiratory-to-expiratory (I/E) ratio of 1:2; and positive end-expiratory pressure (PEEP), 5 cmH_2O. Lactated Ringer's solution was infused at 15 ml·kg^{-1}·h^{-1}, and anesthesia and muscle relaxation were maintained with continuous infusions of pentobarbital sodium 5 mg·kg^{-1}·h^{-1} and pancuronium bromide 0.2 mg·kg^{-1}·h^{-1} via an ear vein. The internal carotid artery was cannulated to aspirate blood samples for blood gas analysis and arterial pressure (AP) monitoring after an injection of 300 U heparin (Novo Nordisk, Copenhagen, Denmark). Normal saline solution, including 2 U·ml^{-1} heparin, was infused at 5 ml·h^{-1} to compensate for blood sampling. These procedures were performed in rigorously sterile conditions.

AP was measured with a pressure transducer (Transpac Monitoring Kit; Abbott Critical Care Systems, North Chicago, IL, USA). The signals were amplified (AP-641G, AR-601G; Nihon Kohden, Tokyo, Japan) and led to an analog–digital converter (DI-220; Dataq Instruments, Akron, OH, USA). Signals for airway pressure (Paw), flow, and V_T from the Servo 300 were also led to the analog-digital converter, and recorded in the computer using data acquisition software (Windaq; Dataq Instruments). Subsequent data analysis was performed with dedicated software (Windaq playback, Dataq Instruments). Body temperature (BT) was monitored in the rectum and maintained at around 39°C by warming the body with a heating pad.

After baseline blood gas analysis was performed with a calibrated blood gas analyzer (ABL505; Radiometer, Copenhagen, Denmark), the lungs were ventilated with a PCV level of 25 cmH_2O; PEEP, 0 cmH_2O; f, 20 breaths·min^{-1}; I/E ratio, 1:4; and $F_{I_{O_2}}$, 1.0.

After Pa_{O_2} decreased to below 300 mmHg, the animals were randomly assigned to two groups. The P group (n = 7) received pressure-regulated volume-control ventilation (PRVCV; decelerating inspiratory flow): V_T, 20 ml·kg^{-1}; PEEP, 5 cmH_2O; f, 20 breaths·min^{-1}; I/E ratio, 1:4; and $F_{I_{O_2}}$, 1.0. The V group (n = 7) received volume-control ventilation (VCV; constant inspiratory flow); V_T, 20 ml·kg^{-1}; PEEP, 5 cmH_2O; f, 20 breaths·min^{-1}, I/E ratio, 1:1; and $F_{I_{O_2}}$, 1.0. In PRVCV, pressure levels were regulated automatically to maintain the preset V_T. Arterial blood gases and hemodynamic data were sampled every 30 min. We measured intrinsic PEEP levels, using the expiratory hold function of the ventilator, every 60 min, three times on each occasion. Similarly, inspiratory plateau pressure (Pplat) was measured every 60 min by using the inspiratory hold function of the ventilator. Each occlusion was held for at least 2.5 s. The static compliance of the respiratory system (Crs) was calculated by the formula: V_T/(Pplat – total PEEP).

After 240 min of mechanical ventilation, immediately prior to our harvesting of the trachea and lung, each animal was killed by the injection of 100 mg·kg^{-1} pentobarbital sodium. The animals were exsanguinated as thoroughly as possible, after which the chest was carefully opened for en-bloc removal of the lungs and trachea. The right lungs were used for the determination of wet and dry weights and the left lungs for histological examination. The right lungs were weighed immediately after excision and put into an oven (Sanyo, Osaka, Japan) at 50°C for 72 h and weighed again to obtain the dry weight.

The left lungs were fixed by immersion in 10% buffered neutral formalin at a hydrostatic pressure of 15 cmH_2O and the specimens were floated in a fixative for 48 h. The lungs were cut into 5-mm-thick coronal slices from apex to base. From each paraffin-embedded sample, 3 µm slices were taken. The sections of the lung tissues in the upper and lower lobes were stained with hematoxylin-eosin and examined by a pathologist who was blinded to the protocol and experimental groups. Lung injury was scored for four characteristics: alveolar congestion; hemorrhage; infiltration or aggregation of neutrophils in the airspace or the vessel wall; and thickness of the alveolar wall/hyaline membrane formation [10]. Each item was scored on a five-point scale: 0, mini-

mal (little) damage; 1, mild damage; 2, moderate damage; 3, severe damage, and 4, maximal damage. Normal histology would be represented by a zero score, while a score of 16 represented maximal damage.

Lung injury scores are presented as median (range) values, and the other data are presented as means ± SD. Parametric data were analyzed with one-way or two-way analysis of variance (ANOVA), followed by a post-hoc analysis with the Tukey honestly significant difference test. Using a statistics software package (Statistica 5.5; StatSoft, Tulsa, OK, USA), lung injury scores and wet-to-dry ratios were examined with Kruskall-Wallis ANOVA median testing, followed by a post-hoc analysis with the Mann-Whitney *U*-test. Statistical significance was accepted at $P < 0.05$.

Results

At the beginning of mechanical ventilation, the two groups had similar baseline characteristics for body weight, pH, Pa_{O_2}, Pa_{CO_2}, mean AP (MAP), V_T, and Crs (Table 1). The time taken for Pa_{O_2} to decrease below 300 mmHg did not differ significantly between the groups.

Figure 1 shows typical flow and Paw tracings for both groups. The flow waveform of PRVCV was decelerating, while that of VCV was square. At the start of either ventilatory mode, Pa_{O_2}, Pa_{CO_2}, MAP, and BT were similar, and the degree of lung injury induced by alveolar overdistension was assumed to be similar in the two groups. Table 2 shows the ventilatory and respiratory parameters of each group at both the start and the end of the protocol. Throughout the protocol, peak inspiratory pressure (PIP) and mean inspiratory flow were significantly higher in the P group than in the V group ($P < 0.05$). PIP in the P group increased gradually and was significantly higher at the end of the protocol than that in the V group. Intrinsic PEEP was not detected in any animal. No other significant differences in ventilatory characteristics were found between the groups.

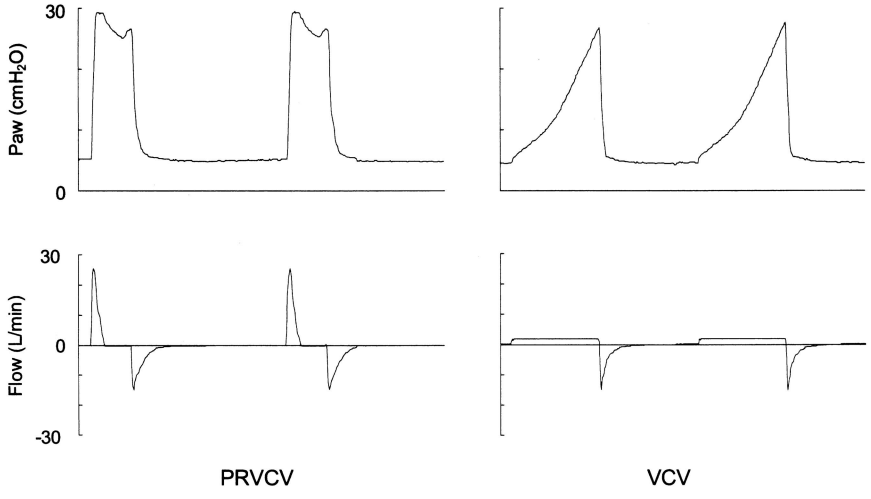

Fig. 1. Typical flow and airway pressure (*Paw*) tracings from both groups at the start of either mode of mechanical ventilation. *PRVCV*, pressure-regulated volume-control ventilation (P group); *VCV*, volume-control ventilation (V group)

Table 1. Basic characteristics of the animals in each group

	V group	P group
Number of animals	7	7
Weight (g)	2729 ± 170	2704 ± 105
Beginning of the experiment		
pH	7.49 ± 0.06	7.49 ± 0.05
Pa_{O_2} (mmHg)	509.8 ± 30.2	517.6 ± 24.9
Pa_{CO_2} (mmHg)	32.0 ± 2.0	33.0 ± 2.0
BE	0.7 ± 1.9	2.9 ± 3.7
MAP (mmHg)	99.0 ± 6.0	103.0 ± 5.0
V_T (ml·kg^{-1})	37.0 ± 3.1	36.0 ± 0.8
Crs (ml·cmH_2O^{-1})	4.2 ± 0.3	4.2 ± 0.5
Time taken to cause lung injury (min)	180 ± 108	179 ± 40

Values are expressed as means ± SD
MAP, mean arterial pressure; BE, base excess; V_T, tidal volume; Crs, static compliance of the respiratory system

Table 2. Ventilatory and respiratory parameters of the animals at the start and at the end of the protocol mechanical ventilation in each group

	At start of each mode of ventilation		At end of the protocol	
	V group	P group	V group	P group
PIP (cmH_2O)	25.7 ± 1.8	2.51 ± 1.2	28.0 ± 2.6[1]*	28.0 ± 1.9[2]*
mPaw (cmH_2O)	9.6 ± 0.9	9.1 ± 1.0	9.7 ± 0.8	9.6 ± 1.0[2]*
Total PEEP (cmH_2O)	4.9 ± 0.2	4.8 ± 0.3	4.7 ± 0.3	4.7 ± 0.2
Peak flow ($l \cdot min^{-1}$)	1.2 ± 0.2	26.7 ± 5.0[3]*	1.2 ± 0.2	29.1 ± 6.2[2*;3]*
Mean flow ($l \cdot min^{-1}$)	1.2 ± 0.2	4.3 ± 0.3[3]*	1.1 ± 0.1	4.3 ± 0.3[3]*
V_T ($ml \cdot kg^{-1}$)	20.0 ± 0.4	20.1 ± 0.3	19.9 ± 0.4	19.9 ± 0.3
Crs ($ml \cdot cmH_2O^{-1}$)	3.2 ± 0.4	2.8 ± 0.3	3.1 ± 0.5	2.6 ± 0.3[2]*

$P < 0.05$, two-way ANOVA and Tukey's post hoc test [1]* vs V group at start; [2]* vs P group at start; [3]* vs V group for the specific period
Values are expressed as means ± SD
PIP, peak inspiratory pressure; mPaw, mean airway pressure; total PEEP, total positive end-expiratory pressure; V_T, tidal volume; Crs, static compliance of the respiratory system

Table 3. Blood gas analysis and body temperature at the start and at the end of the protrocol mechanical ventilation of the animals in each group

	At start of each mode of ventilation		At end of protocol	
	V group	P group	V group	P group
pH	7.39 ± 0.03	7.42 ± 0.04	7.40 ± 0.04	7.38 ± 0.05
Pa_{O_2} (mmHg)	296 ± 48	295 ± 27	373 ± 90	280 ± 129
Pa_{CO_2} (mmHg)	38 ± 2	40 ± 3	35 ± 3	40 ± 4
MAP (mmHg)	91 ± 5	92 ± 6	91 ± 8	98 ± 8
BE	–1.2 ± 2.4	1.1 ± 3.6	–3.4 ± 2.6	–1.4 ± 2.6[2]*
BT (°C)	39.3 ± 0.7	38.9 ± 0.8	39.6 ± 0.5[1]*	39.3 ± 0.6[2]*

$P < 0.05$, two-way ANOVA and Tukey's post hoc test [1]* vs V group at start; [2]* vs P group at start
Values are expressed as means ± SD
MAP, mean arterial pressure; BE, base excess; BT, body temperature

No significant differences in blood gas results were found between the groups (Table 3). Neither MAP nor BT differed significantly between the groups, and, in both groups, BT had increased at the end of the protocol. The wet-to-dry ratio in the P group was significantly higher than that in the V group ($P < 0.05$; Table 4). More animals in the P group than in the V group ended with a Pa_{O_2}/FI_{O_2} ratio of less than 200 mmHg. For both groups, upper, lower, and overall histological lung injury scores were similar (see examples of histology in the two groups in Fig. 2).

Table 4. Oxygenation, wet-to-dry ratio, and lung injury score of each group at the end of the ventilation protocol

	V group	P group	*P*
Pa_{O_2}/FI_{O_2} ratio <200	0/7	3/7	0.06
Wet-to-dry ratio	6.3 ± 0.5	7.7 ± 0.9	<0.01
Lung injury score			
Total	2	4	0.60
Upper lobe	2	2	0.85
Lower lobe	6	8	0.28

Except for the wet-to-dry ratio (mean ± SD), values are expressed as medians. Lung injury was scored according to the following four items: alveolar congestion; hemorrhage; infiltration or aggregation of neutrophils in the airspace or the vessel wall; and thickness of the alveolar wall/hyaline membrane formation

Discussion

The major findings of the present study were that more animals in the P group than in the V group ended the protocol with a Pa_{O_2}/FI_{O_2} ratio of less than 200 mmHg and with higher wet-to-dry lung tissue ratios. No differences between the groups were revealed in either histological examination or in respiratory mechanics.

Few studies have compared the effect of inspiratory flow on VILI. Rich et al. [6] suggested that, in sheep, slow peak inspiratory flow protected against VILI even with high PIP. Maeda et al. [7] showed that deteriorations in gaseous exchange and respiratory mechanics were marked when there were injurious levels of high peak inspiratory flow, and this research group (Nishimura et al. [11]) concluded that, as well as high V_T and body position, peak inspiratory flow played a role in

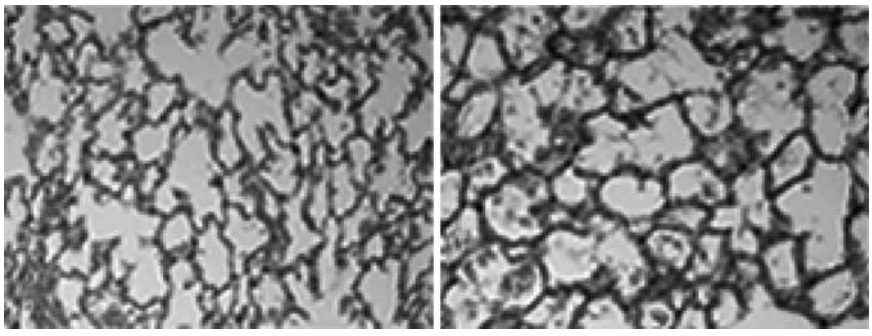

Fig. 2. Slices of the lower lobe in **a** the V group and **b** the P group. Congestion, hemorrhage, infiltration, or aggregation of neutrophils in the airspace or the vessel wall, and thickness of the alveolar wall/hyaline membrane formation were shown in both groups. **a** and **b** ×100

the development of VILI in animal models [7]. Kotani et al. [8] discovered that, in comparison with cells involved in low inspiratory flow, mild overstretch of perfused lungs during high inspiratory flow resulted in greater inflammatory signaling by the cells most affected by strong turbulent airflow. These studies, however, investigated the effect of inspiratory flow on the development of VILI in normal animals. In patients with ALI/ARDS, mechanical ventilation is started after the lungs are injured. In order to investigate the effect of inspiratory flow on injured lungs, we first damaged the lungs of rabbits with high inflation pressure. After lung injury developed, we decreased the V_T setting to 20 ml·kg^{-1}, which was lower than the level used in many previous animal studies [7,11]. PIP was kept at around 25 cmH_2O for both groups, and was lower than that in other published animal studies, while V_T was still excessively higher than that in clinical practice. Once the lungs were injured, mechanical ventilation kept on injuring the lungs, and this may explain why the histological scores of our two groups were similar. Injured lungs are considered to be more vulnerable to overstretch, and this may also explain why the histological difference was not significant between the groups. We applied 5 cmH_2O of PEEP, a level which was not high enough for opening all the alveoli, but which has been found to be protective against VILI in animal models [12]. In our study, the wet-to-dry ratio was significantly different between the groups, and this showed that the lung injuries were more severe in the P group than in the V group, although the histological difference was scant.

In the present study, f and V_T were maintained at the same level for all animals. To compare the effect of peak inspiratory flow, we used PRVCV with an I/E ratio of 1:4 and VCV with an I/E ratio of 1:1, resulting in different I/E ratios as well as different inspiratory flow levels for the two groups. Casetti et al. [13] reported that, during high-pressure/high-volume mechanical ventilation, increasing inspiratory time was associated with changing variables indicative of increasing lung injury in a rat model. A computed tomography (CT) scan study has revealed that the area of overinflation is greatest in pressure-controlled inverse-ratio ventilation [14]. In the P group in the present study, the short inspiratory time could have been protective against VILI.

More animals in our P group than in the V group ended the protocol with a $Pa_{O_2}/F_{I_{O_2}}$ ratio of less than 200. Dembinski et al. [15] have reported that, in a lung lavage pig model, constant flow provides more favorable ventilation, perfusion distribution, and oxygenation than decelerating waveforms or a combination of deceleration and constant waveforms. Both in the present study and in that study [15], inspiratory flow was higher in the groups with a decelerating waveform than in those with a square waveform. The greater number of animals with a low $Pa_{O_2}/F_{I_{O_2}}$ ratio in our P group may have been due to the decelerating flow waveform. It is unclear which is more important to induce VILI, the waveform or the inspiratory flow.

The wet-to-dry ratio has been used as a factor in evaluating lung edema, and the ratio did differ for our two groups, even though the histological scores did not. Alveolar overstretch causes both alveolar epithelial and vascular endothelial damage, which results in fluid leakage into the alveolar spaces [4]. Fluid accumulation in the alveoli starts at a very early phase of VILI, and Crs decreases as fluid accumulation increases. Usually, however, Crs decreases abruptly when the volume of accumulated fluid exceeds the threshold. Although neither the histological score nor compliance was different in our groups, the different wet-to-dry ratio results may have been indicative of incipient VILI. While we found that PRVCV induced greater accumulation of alveolar fluid than VCV, 4 h of mechanical ventilation may have been too short to result in Crs and/or histological differences between the groups.

In the present study, we choose PRVCV and VCV to maintain V_T constant throughout the study. If we had chosen simple PCV, V_T would have decreased as the lungs were injured and Pa_{cO_2} would have increased. Hypercapnia is considered to be protective of the lung, and we chose PRVCV as high inspiratory flow ventilation [16]. However, PIP increased as the lung was injured in the group with PRVCV. In addition, the flow waveform

was decelerating with PRVCV, while it was square with VCV. The I/E ratio differed between the two groups. In the present study, therefore, not only peak inspiratory flow but also other factors could have influenced the results.

In our experimental design, we compared two inspiratory peak flows at different I/E ratios at 4-h observation after inducing lung injury, and these conditions may not have been suitable for detecting a histological difference. It may be necessary to carry out an investigation to compare groups with the same type of flow waveform and the same I/E ratio, and to extend the observation time of the experiment and increase the number of animals.

In summary, we investigated the effect of inspiratory flow on the development of VILI in rabbits with damaged lungs. High peak inspiratory flow in the group with PRVCV with high V_T ($20\,ml \cdot kg^{-1}$) worsened oxygenation and resulted in a higher wet-to-dry ratio than that in the VCV group. High inspiratory flow may be harmful when V_T and/or PIP are high.

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