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Effects of Peak Inspiratory Flow on Development of Ventilator-induced Lung Injury in Rabbits

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Background: **A lung-protecting strategy is essential when ventilating acute lung injury/acute respiratory distress syndrome patients. Current emphasis is on limiting inspiratory pressure and volume. This study was designed to investigate the effect of peak inspiratory flow on lung injury.**

Methods: **Twenty-four rabbits were anesthetized, tracheostomized, ventilated with a Siemens Servo 300, and randomly assigned to three groups as follows: 1) the pressure regulated volume control group received pressure-regulated volume control mode with inspiratory time set at 20% of total cycle time, 2) the volume control with 20% inspiratory time group received volume-control mode with inspiratory time of 20% of total cycle time, and 3) the volume control with 50% inspiratory time group received volume-control mode with inspiratory time of 50% of total cycle time. Tidal volume was 30 ml/kg, respiratory rate was 20 breaths/min, and positive end-expiratory pressure was 0 cm H_2O. After 6 h mechanical ventilation, the lungs were removed for histologic examination.**

Results: **When mechanical ventilation started, peak inspiratory flow was 28.8 ± 1.4 l/min in the pressure regulated volume control group, 7.5 ± 0.5 l/min in the volume control with 20% inspiratory time group, and 2.6 ± 0.3 l/min in the volume control with 50% inspiratory time group. Plateau pressure did not differ significantly among the groups. Gradually during 6 h, Pao_2 in the pressure regulated volume control group decreased from 688 ± 39 to a significantly lower 304 ± 199 mm Hg ($P < 0.05$) (mean ± SD). The static compliance of the respiratory system for the pressure regulated volume control group also ended significantly lower after 6 h ($P < 0.05$). Wet to dry ratio for the pressure regulated volume control group was larger than for other groups ($P < 0.05$). Macroscopically and histologically, the lungs of the pressure regulated volume control group showed more injury than the other groups.**

Conclusion: **When an injurious tidal volume is delivered, the deterioration in gas exchange and respiratory mechanics, and lung injury appear to be marked at a high peak inspiratory flow.**

THE potential detrimental effect of ventilation on the lungs has been concerned for many years. Avoidance of excessive tidal volume (V_T) reduces the risk of ventilator-associated lung injury resulting from overstretch of the lung and improves the mortality of patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS).[1–4] Overstretch of the lung is not, however, the only mechanism of ventilator-associated lung injury, in which shear forces are believed to be an important factor. Mead *et al*. have suggested that the pressure across an atelectatic region adjacent to open lungs can reach approximately 140 cm H_2O when transpulmonary pressure is 30 cm H_2O.[5]

Maintenance of spontaneous breathing in mechanically ventilated patients is considered to be a good ventilatory strategy[6] because contraction of the diaphragm is helpful for keeping the lungs open, especially in the dependent and caudal regions. In some severe ARDS patients it is difficult to keep spontaneous breathing as a result of the altered lung mechanics. Even in this case many clinicians prefer pressure-control ventilation (PCV) because it is easy to control peak airway pressure with PCV. The down side is that high peak inspiratory flow of PCV may aggravate lung injury possibly with greater shear forces than lower peak inspiratory flow of volume control ventilation.[7,8] We hypothesized that, in a rabbit model, high peak inspiratory flow of PCV would be associated with the development of ventilator-induced lung injury (VILI).

Materials and Methods

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 care and use of laboratory animals.

Adult male New Zealand white rabbits (weighing 2.8 ± 0.2 kg) were anesthetized *via* an ear vein with an injection of 50–60 mg pentobarbital and were set in a supine position on a heating pad. The tracheostomy was performed using a midline incision of the neck after infiltration of local anesthesia (1.5–2 ml of 1% lidocaine) at the level of the second or third tracheal cartilage. After insertion of a 4 mm inner diameter endotracheal tube (Blue Line tracheostomy tube; SIMS Portex, Kent, UK) into the trachea, the trachea was tied to prevent air leak. Then the animals were paralyzed with pancuronium bromide and mechanical ventilation was started with a Siemens Servo 300 ventilator (Siemens-Elema AB, Solna, Sweden) with the following settings: PCV pressure 10 cm H_2O; F_{IO_2} 1.0; respiratory rate 20 breaths/min with inspiratory time (T_i) at 50% of total cycle time (T_{tot}); and positive end-expiratory pressure (PEEP) 0 cm H_2O. Anesthesia and muscle relaxation were maintained with pancuronium bromide (0.2 $mg \cdot kg^{-1} \cdot h^{-1}$) and sodium pentobarbital (5 $mg \cdot kg^{-1} \cdot h^{-1}$).

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The internal carotid artery was cannulated with a 20-gauge catheter (Angiocath 20; Becton Dickinson Vascular Access, Sandu, Utah) and received a Multiparameter sensor (Paratrend 7+™; Diametrics Medical Ltd., High Wycombe, UK) through the catheter for continuous intraarterial blood gas monitoring of Pa_{O_2}, pH, Pa_{CO_2}, and temperature. The data from this sensor was sampled at 1-min intervals and stored on a personal computer. Animals with Pa_{O_2} less than 500 mm Hg with these settings of ventilator were excluded from this study. As a result a total of 24 animals were investigated.

Arterial pressure was measured with a pressure transducer (TRANSPAC Monitoring Kit; Abbott Critical Care Systems, North Chicago, IL). The signals were amplified (AP-641G, AR-601G; Nihon Kohden, Tokyo, Japan) and stored on the computer *via* an analog-digital converter (DI-220, Dataq Instruments, Akron, OH). Lactated Ringer's solution was administered at a rate of 10 $ml \cdot kg^{-1} \cdot h^{-1}$, and the rate was titrated to maintain blood pressure within the range of ± 10% of initial values.

Before starting the study, a functional check of the ventilator was made according to manufacturer instructions, and then the pressure and flow transducers of the ventilator were calibrated with independent devices. The signals for pressure, flow and V_T were monitored with the ventilator and similarly stored *via* the converter to avoid the dead space resulting from the sensors. Recording of signal data on the computer system was managed using data acquisition software (WinDaq, Dataq Instruments, Akron, OH). Subsequent data analysis was performed with dedicated software (WinDaq playback, Dataq Instruments, Akron, OH).

Experimental Protocol

The animals were randomly assigned to one of three groups according to ventilatory strategy: the pressure regulated volume control (PC) group (n = 8) received pressure-regulated volume control mode with T_i at 20% of T_{tot}; the volume control with 20% T_i (VC_{20}) group (n = 8) received volume-control mode with T_i at 20% of T_{tot}; and the volume control with 50% T_i (VC_{50}) group (n = 8) received volume-control mode with T_i at 50% of T_{tot}. Other, common, settings for each animal were as follows: V_T, 30 ml/kg; respiratory rate, 20 breaths/min; and PEEP, 0 cm H_2O. CO_2 gas was added to maintain Pa_{CO_2} at 35–45 mm Hg. The inspiratory fraction of CO_2 was kept constant throughout the study.

Every 30 min, we measured intrinsic-PEEP levels using the expiratory hold button of the ventilator to perform end-expiratory airway occlusion. Similarly, using the inspiratory hold button of the ventilator, plateau pressure ($P_{plateau}$) was also measured every 30 min. To calculate the static compliance of the respiratory system (C_{rs}), end-inspiratory occlusion was repeated three times. Each occlusion was held for at least 2.5 s. From the recorded curves, C_{rs} was calculated as $V_T/(P_{plateau} -$ intrinsic-PEEP).

All animals were ventilated for 6 h and then killed with a large dose of pentobarbital sodium. Then the animals were exsanguinated as much as possible, the chest was carefully opened, and the lungs and trachea were removed en bloc. The right lungs were used for comparative measurement of wet and dry weights and the left for histologic analysis. The right lungs were weighed immediately after excision and put in an oven (Sanyo, Osaka, Japan) at 37°C for 48 h and weighed again to obtain the dry weight for calculation of wet to dry weight ratio. The left lungs were fixed by intratracheal insufflation with 10% formalin at a hydrostatic pressure of 15 cm H_2O and the specimens were floated in a fixative for 48 h. The lungs were cut into slices 5 mm thick in a coronal fashion from apex to base. Samples were systematically taken at a distance of 1.5 cm from the hilum in the lower lobe and embedded in paraffin. From each sample, 3-μm slices were stained with hematoxylin and eosin and Masson trichrome for microscopic examination. Experimental group information was unknown to the microscopist who evaluated the samples. Criteria were based on total score of four parameters: alveolar congestion, hemorrhage, infiltration or aggregation of neutrophils in airspaces or vessel walls, and thickness of alveolar wall/hyaline membrane formation by using a damage scale of 0 to 4 as follows: 0, minimal or no damage; 1, mild damage (less than 25% of the field); 2, moderate damage (25% to 50% of the field); 3, severe damage (50% to 75% of the field); 4, maximal damage (more than 75% of the field).[9] Therefore, a total score of 0 presented normal histology and a score of 16 presented maximal damage. The examination was again performed after 6 months. Difference of total score between the two examinations was less than 10% on each slide; mean values of the two examinations were used in the results.

Data Analysis

Results are presented as mean ± SD. We used two-way analysis of variance for repeated measures to determine the statistical significance of group differences in blood gases and respiratory parameters at different time points as well as differences among measurement points in each group. One-way analysis of variance was used to determine the statistical significance of group differences in lung weight. When statistical significance was indicated, it was further examined by *post hoc* analysis (Tukey honest significant difference test). Lung injury scores were analyzed by Kruskal-Wallis nonparametric analysis of variance followed by the Mann–Whitney *U* test. A statistical software package (STATISTICA 5.5;

Table 1. Ventilatory Parameters, Blood Gas Analysis, and Body Temperature of Each Group of Animals at Start of Mechanical Ventilation and at End of the Protocol

	At start of mechanical ventilation			At end of the protocol		
	PC	VC_{20}	VC_{50}	PC	VC_{20}	VC_{50}
PIP (cm H_2O)	22 ± 1	27 ± 2†	23 ± 2‡	31 ± 4*	30 ± 3*	24 ± 3†‡
Paw mean (cm H_2O)	4.9 ± 0.4	3.1 ± 0.2†	5.1 ± 0.3‡	6.4 ± 0.9*	3.8 ± 0.5*†	6.1 ± 2.0*‡
Intrinsic PEEP (cm H_2O)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Peak flow (L/min)	28.8 ± 1.4	7.5 ± 0.5†	2.6 ± 0.3†‡	35.6 ± 2.8*	7.4 ± 0.4†	2.5 ± 0.3†‡
Mean flow (L/min)	7.6 ± 0.3	7.2 ± 0.5	2.3 ± 0.3†‡	7.7 ± 0.4	7.1 ± 0.5	2.4 ± 0.3†‡
V_T (mL/kg)	29.9 ± 0.2	29.8 ± 0.3	29.8 ± 0.3	29.9 ± 0.3	29.8 ± 0.3	29.9 ± 0.3
pH	7.46 ± 0.07	7.49 ± 0.05	7.48 ± 0.02	7.34 ± 0.09*	7.40 ± 0.03*	7.41 ± 0.05
Pa_{O_2} (mm Hg)	688 ± 39	711 ± 34	699 ± 33	304 ± 199*	589 ± 112*†	620 ± 214†
Pa_{CO_2} (mm Hg)	42 ± 2	42 ± 2	41 ± 4	51 ± 8*	44 ± 3	43 ± 7
ABP (mm Hg)	107 ± 10	113 ± 10	104 ± 5	102 ± 7*	93 ± 9*	93 ± 9*
BT (°C)	39.6 ± 0.4	39.7 ± 0.5	39.6 ± 0.5	39.9 ± 0.9	40.1 ± 0.6	40.0 ± 1.0

Data are presented as mean ± SD.

ABP = mean arterial blood pressure; BT = body temperature; Intrinsic PEEP = intrinsic positive end expiratory pressure; Paw mean = mean airway pressure; PC = pressure-regulated volume control mode with inspiratory time at 20% of total cycle time; PIP = peak inspiratory pressure; VC_{20} = volume-control mode with inspiratory time at 20% of total cycle time; VC_{50} = volume-control mode with inspiratory time at 50% of total cycle time; V_T = tidal volume.

StatSoft Inc., Tulsa, OK) was used, and significance was set at $P < 0.05$.

Results

In 24 rabbits randomly allotted to each of the three groups we found that at the beginning of mechanical ventilation, each group had similar baseline characteristics for body weight, Pa_{O_2}, Pa_{CO_2}, pH, and mean arterial pressure (table 1).

Figure 1 shows typical flow and airway pressure tracings of each group at the beginning of mechanical ventilation. For each animal throughout the protocol, V_T was maintained at 30 ml/kg. Peak inspiratory pressure (PIP) for the VC_{20} group was significantly higher than for the PC group and the VC_{50} group ($P < 0.05$) at the start of mechanical ventilation, and PIP for the VC_{50} group

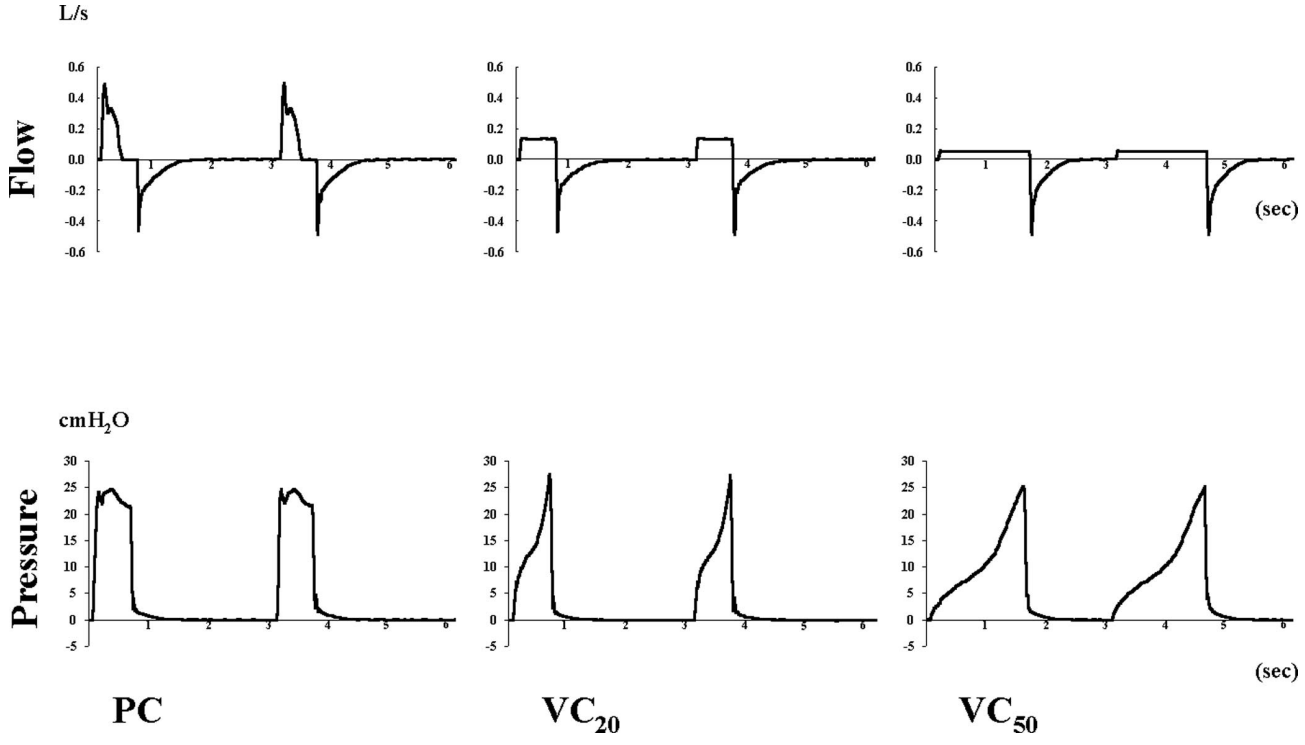

Fig. 1. (*Upper panel*) Representative flow tracings of each group at the beginning of the mechanical ventilation. (*Lower panel*) Representative pressure tracings of each group at the beginning of the mechanical ventilation. *PC* = pressure-regulated volume control mode with inspiratory time at 20% of total cycle time; *VC_{20}* = volume-control mode with inspiratory time at 20% of total cycle time; and *VC_{50}* = volume-control mode with inspiratory time at 50% of total cycle time.

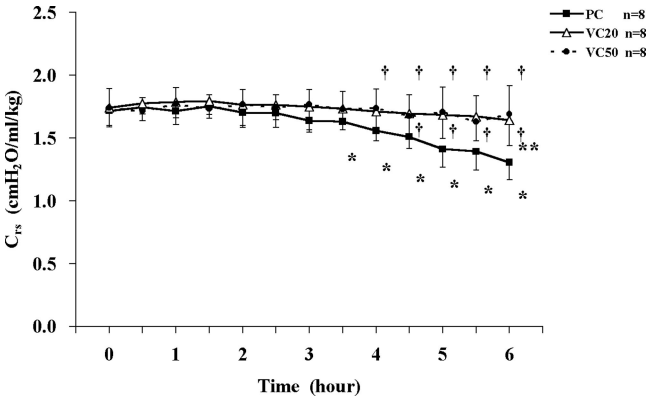

Fig. 2. Time course of changes in respiratory system compliance of the three groups. C_{rs} = compliance of the respiratory system; *PC* = pressure-regulated volume control mode with inspiratory time at 20% of total cycle time; VC_{20} = volume-control mode with inspiratory time at 20% of total cycle time; and VC_{50} = volume-control mode with inspiratory time at 50% of total cycle time. All values are mean ± SD *Significant difference ($P < 0.05$) compared with 0 min in the PC group; **significant difference ($P < 0.05$) compared with 0 min in the VC_{20} group; †significant difference ($P < 0.05$) compared with the PC group at each measurement point.

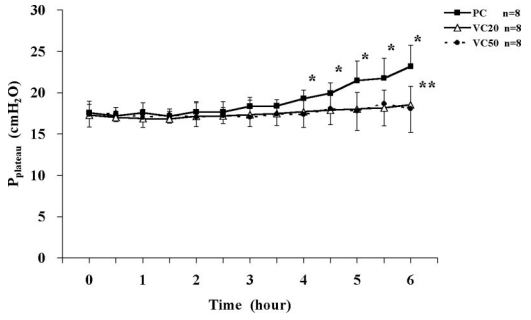

Fig. 3. Time course of changes in plateau pressure of the three groups. $P_{plateau}$ = plateau pressure; *PC* = pressure-regulated volume control mode with inspiratory time at 20% of total cycle time; VC_{20} = volume-control mode with inspiratory time at 20% of total cycle time; and VC_{50} = volume-control mode with inspiratory time at 50% of total cycle time. All values are mean ± SD *Significant difference ($P < 0.05$) compared with 0 min in the PC group; **significant difference ($P < 0.05$) compared with 0 min in the VC_{20} group.

was significantly lower than for the PC group and the VC_{20} group at end of the protocol ($P < 0.05$). PIP for the PC group and the VC_{20} group at the end of the protocol significantly increased compared with those at start of mechanical ventilation. Mean airway pressure (Paw mean) for the VC_{20} group was significantly lower than for the PC group and the VC_{50} group throughout the 6 h of ventilation ($P < 0.05$). Paw mean for the three groups at end of the protocol significantly increased compared with those at start of mechanical ventilation ($P < 0.05$). Intrinsic-PEEP did not occur in any animals. In the PC group, peak inspiratory flow at end of the protocol significantly increased compared with that at start of mechanical ventilation ($P < 0.05$). Mean flow of the VC_{50} group was significantly lower than the other groups ($P < 0.05$), and mean flows of the PC group and the VC_{20} group were similar. Tidal volumes of the three groups did not differ significantly throughout the 6 h of ventilation. After 6 h, Pao_2 and pH for the PC group and the VC_{20} group decreased significantly and $Paco_2$ for the PC group increased significantly compared to those at the start ($P < 0.05$) (table 1).

At the start of mechanical ventilation, $P_{plateau}$ and C_{rs} of the three groups did not differ significantly; after 3.5 h of mechanical ventilation C_{rs} of the PC group decreased significantly ($P < 0.05$) (fig. 2). This decrease in C_{rs} was followed by increased $P_{plateau}$ in the PC group, which was significantly higher after 4 h of mechanical ventilation than at the start ($P < 0.05$) (fig. 3).

Figure 4 shows the wet to dry ratio of each group. After 6 h ventilation the lungs of the PC group had more water content than the other groups ($P < 0.05$).

The lungs of the PC group exhibited gross damage, including edema with distinct petechial hemorrhages on the surface. The lungs of the VC_{20} group were less damaged than those in the PC group. In the VC_{50} group most lungs were pink and neither edematous nor hemorrhagic. Lung injury scores were larger in the PC group than in the VC_{20} group and the VC_{50} group ($P < 0.05$) (fig. 5). Microphotographs representative of the lungs in the three groups are shown in figure 6A, B and C. Alveolar and interstitial edema, alveolar hemorrhage, and infiltration of neutrophils are observed in the PC group (fig. 6A). Alveolar wall thickness is observed in some of the fields in the VC_{20} group (fig. 6B) and almost no histologic abnormality is observed in the VC_{50} group (fig. 6C).

Discussion

Major findings of the current study are as follows: 1) PCV was associated with more lung damage, manifested by hypoxemia and histologic damage, than the low flow of volume-control ventilation (VCV) with the same V_T

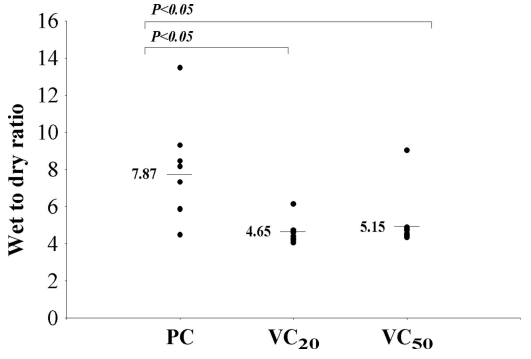

Fig. 4. Wet to dry ratios of the three groups. Short horizontal lines show means of each group. *PC* = pressure-regulated volume control mode with inspiratory time at 20% of total cycle time; VC_{20} = volume-control mode with inspiratory time at 20% of total cycle time; and VC_{50} = volume-control mode with inspiratory time at 50% of total cycle time.

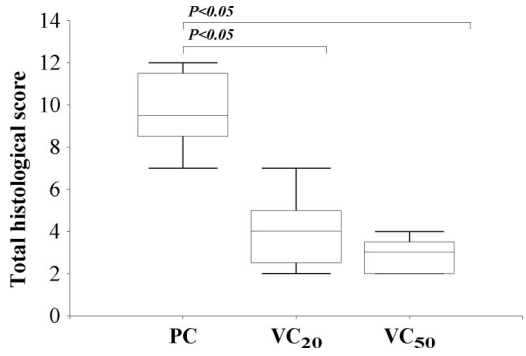

Fig. 5. Lung injury score of the three groups. *Boxes* = 25th and 75th percentiles, and the median value; whiskers = minimum and maximum values. *PC* = pressure-regulated volume control mode with inspiratory time at 20% of total cycle time; VC_{20} = volume-control mode with inspiratory time at 20% of total cycle time; and VC_{50} = volume-control mode with inspiratory time at 50% of total cycle time.

and the same $P_{plateau}$; 2) between the two settings of VCV (VC_{20} and VC_{50} groups), there was no difference in oxygenation and histologic damage of the lungs.

These results may suggest that there is some threshold in peak inspiratory flow that becomes injurious to the lungs in ventilating with large V_T. A possible explanation of the difference in lung injury between the PC group and the VCV groups is the shear stress during inspiration on the airways and alveoli, although this was not proved in our study.

A few studies have reported the effect of peak inspiratory flow on VILI. Comparison of findings is difficult, however, because the ventilatory settings were not the same. Investigating the effect of peak inspiratory flow on VILI in sheep, Rich *et al.*[7] compared two levels of PCV (20 and 45 cm H_2O) at 5 breaths/min and 15 breaths/min of respiratory rates with VCV of 15 l/min of peak inspiratory flow at 5 breaths/min. VCV induced the least damage even at high PIP; they concluded that slow peak inspiratory flow protected against VILI. Although PIP was 50 cm H_2O in both VCV and PCV of 45 cm H_2O, in neither group of animals was V_T controlled. It is possible that $P_{plateau}$ might have been higher in PCV. With 20 cm H_2O of PCV, lung injury was less, even though the mean flow of PCV 20 cm H_2O and 45 cm H_2O was the same.

In the current study, respiratory rate and V_T were same for all animals. Meanwhile in the PC group and the VC_{20} group, T_i was same, and the flow waveform was square in the VC_{20} group and the VC_{50} group. In the PC group, the flow waveform was decelerating pattern. We did not compare decelerating waveform in VCV, so it still remains to be clarified whether peak inspiratory flow itself or flow waveform is the more important factor in VILI. There are some reports relating inspiratory flow profiles to gas exchange, work of breathing, and cardiovascular functions;[8,10,11] however, few studies have investigated the relationship between VILI and inspiratory flow profiles. Peevy *et al.* have investigated the effect of inspiratory flow on microvascular injury in isolated perfusion lungs.[12] Using different ventilatory rates, PIP, T_i, and V_T for different groups, they found that a combination of high PIP and high peak inspiratory flow induced the most severe microvascular damage. Within similar

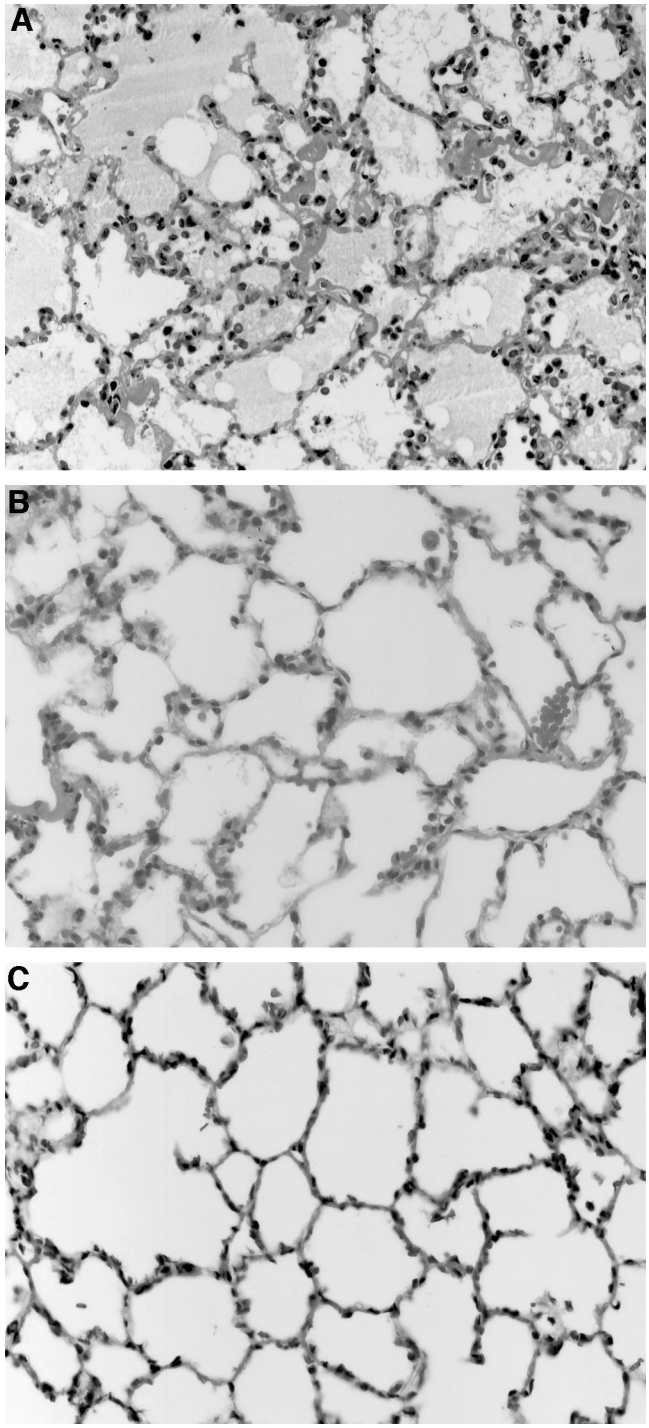

Fig. 6. Microscopic aspects of the lungs of the three groups. (*A*) *PC* = pressure-regulated volume control mode with inspiratory time at 20% of total cycle time; (*B*) VC_{20} = volume-control mode with inspiratory time at 20% of total cycle time; and (*C*) VC_{50} = volume-control mode with inspiratory time at 50% of total cycle time. (HE stain, magnification 200×).

ranges of PIP, high peak inspiratory flow induced more microvascular damage. Consequently, their results suggest that not only overdistension but also peak inspiratory flow range are important in VILI. Their results suggest that high peak inspiratory flow and inspiratory waveform in the PC group might be important to develop VILI.

For PCV we used the pressure-regulated volume control of the Siemens Servo 300. This unique technology maintains preset V_T by controlling pressure control levels. If the mechanics of the patient vary, the ventilator decreases or increases pressure control levels to maintain a constant V_T. In the current study, the pressure control level increased gradually toward the end of the protocol because the lungs were injured and had decreased compliance. Higher inspiratory pressure resulted in more lung injury. If we had chosen simple PCV, V_T decreased along with the development of lung injury and increased $Paco_2$. As a result, the lung damage could have been less. Even with the pressure-regulated volume control, $Paco_2$ increased significantly in the PC group, probably owing to increased dead space in the injured lungs. On the contrary, it is possible that high inspiratory pressure generated by pressure-regulated volume control ventilation maintained Pao_2 at high level. In that case, Pao_2 could have decreased more quickly if we chose simple PCV.

Many animal studies have provided evidence that PEEP protects against VILI.[13,14] At slow peak inspiratory flow, inspiratory time was longer and expiratory time was consequently shorter. This may create intrinsic-PEEP even in healthy lungs and protect the lungs against VILI. To confirm that intrinsic-PEEP was not the reason for lung protection in the VC_{50} group in the current study, we measured intrinsic-PEEP every 30 min using the expiratory hold button and confirmed for all the animals that intrinsic-PEEP was not occurring. Another possibility is the difference in Paw mean. The Paw mean in the VC_{20} group was the lowest one and there was statistically no difference in Paw mean between the PC group and the VC_{50} group. We cannot explain the result of our experiment by Paw mean.

This study was performed using a normal rabbit lung model, which does not reflect the same pathophysiology observed in humans or in ALI/ARDS.[15,16] To induce the lung injury, we chose high V_T (30 ml/kg), which could cause injuries solely as the result of overdistension without involving shear forces.[17,18] Although the V_T range was much higher than that used in clinical settings, many previous animal studies also chose high tidal volumes.[19,20] These studies have been substantially contributing to understanding of the mechanisms of VILI and decreasing of the morbidity and mortality of ALI/ARDS. Even with high V_T, low peak inspiratory flows of VC_{20} and VC_{50} were associated with less lung damage. This shows that peak inspiratory flow actually plays a role in the development of VILI, as well as high V_T, body position,[19] atelectasis,[20] PEEP,[13] and inflammatory cytokines.[9,21–23]

In the current study, we revealed that high peak inspiratory flow in PCV induced significantly more severe lung damage than lower peak inspiratory flows in the VC_{20} and the VC_{50} groups. Oxygenation deteriorated significantly in the PC group. In contrast, oxygenation impairment was absent in the VC_{20} and the VC_{50} groups after at 6 h of mechanical ventilation. Histologic examination discovered diffuse lung damage, with the most severe damage in the PC group. Our results may suggest that there is some threshold in flow, which becomes injurious to the lungs in ventilating with large V_T.

In conclusion, when an injurious V_T is delivered at a higher peak flow, the deterioration in gas exchange, respiratory mechanics, and lung histology appears to be more marked than when it is delivered at a lower peak flow in an animal model.

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