High amplitude bubble continuous positive airway pressure decreases lung injury in rats with ventilator-induced lung injury

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Abstract

Background: Bubble continuous positive airway pressure (BCPAP) has been used in neonates with respiratory distress for decades; however, the optimal setting for BCPAP circuits remains unknown. This study compared the gas exchange efficiency and lung protection efficacy between conventional and high-amplitude BCPAP devices.

Methods: We compared gas exchange, lung volume, and pulmonary inflammation severity among rats with ventilator-induced lung injury (VILI) that were treated with conventional BCPAP (BCPAP with an expiratory limb at 0º), high-amplitude BCPAP (BCPAP with an expiratory limb at 135º), or spontaneous breathing (SB). After mechanical ventilation for 90 minutes, the rats were randomly divided into four groups: a control group (euthanized immediately; n = 3), an SB group (n = 8), and two BCPAP groups that received BCPAP with the expiratory limb at either 0º (n = 8) or 135º (n = 7) for 90 minutes.

Results: The high-amplitude BCPAP group exhibited significantly lower alveolar protein, lung volume, and Interleukin-6 (IL-6) levels than did the SB group. The high-amplitude BCPAP group exhibited significantly lower IL-6 levels than did the conventional BCPAP group. The two BCPAP groups demonstrated no difference in gas exchange efficiency.

Conclusion: High-amplitude BCPAP reduced lung inflammation and alveolar overdistension in rats with VILI after mechanical ventilation was ceased. Thus high-amplitude BCPAP may offer a superior lung protective effect than conventional BCPAP.

Keywords: Amplitude; Bronchopulmonary dysplasia; Bubble continuous positive airway pressure; Lung volume; Ventilator-induced lung injury

1. INTRODUCTION

Mechanical ventilation with high tidal volumes may initiate or exacerbate acute lung injury through ventilator-induced lung injury (VILI).[1,2] The association between mechanical ventilation, pulmonary inflammation, and bronchopulmonary dysplasia (BPD) has been known since the 1970s.[3,4] BPD is a serious complication resulting in high morbidity and mortality for neonates. The incidence of the most severe form of BPD can be reduced by treatment with vitamin A,[5] postnatal and antenatal steroids,[6] and caffeine;[7] however, the overall incidence of BPD had remained stable.[8,9]

Nasal continuous positive airway pressure (NCPAP) can facilitate extubation and reduce prolonged ventilation risk;[10] moreover, it is associated with low BPD incidence.[11] Bubble continuous positive airway pressure (BCPAP), a form of continuous positive airway pressure (CPAP), has been used to treat neonatal respiratory disorders for more than 40 years.[10,12,13] In bubbling NCPAP, the variable frequency and amplitude of pressure oscillations may open unrecruited lung units and improve air exchange. BCPAP is associated with a significantly higher rate of successful extubation and a reduced duration of CPAP support compared with infant flow driver CPAP in infants ventilated for lesser than 14 days.[14] Pillow et al.[15] reported that BCPAP improved gas exchange, lung mechanics, gas mixing efficiency, and lung volume compared with constant-pressure CPAP in an ovine model of preterm lung disease. These data suggest that bubbling supported air exchange in addition to simply delivering CPAP and bulk flow ventilation. In their randomized study, Wu et al.[16] demonstrated that rats with VILI receiving bubble CPAP rather than spontaneous breathing (SB) had reduced alveolar protein levels and lung injury scores. However, the most optimal setting for BCPAP circuit to achieve the most favorable gas exchange efficiency and lung protective effect remains unknown.

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Suki et al. contended that the alveoli recruitment process may benefit from the superimposition of noise on the applied driving pressure, exploiting the phenomenon of stochastic resonance.[17] The principles of stochastic resonance suggest that the amplitude and frequency of superimposed noise can be optimized to achieve the most favorable amplification. Recent in vitro studies have reported that the applied bias flow and lung mechanics, the bubble generator bottle diameter, the expiratory limb angle, and the size and submergence depth of the underwater seal of the expiratory limb of the BCPAP circuit all could influence the magnitude and frequency of the noise transmitted to the lung.[18,19] Diblasi et al. tested the BCPAP circuits with various angles of expiratory limbs and found that the highest amplitude of pressure and volume oscillations were produced by the BCPAP device with an expiratory limb at 135°; thus, it was termed "high-amplitude BCPAP."[20] We designed the current animal study to test the hypothesis that treatment using various types of BCPAP (conventional BCPAP with an expiratory limb at 0° vs high-amplitude BCPAP with an expiratory limb at 135°) after discontinuation of mechanical ventilation in rats with VILI would have different effects on gas exchange efficiency and lung protection.

2. METHODS

2.1. Animal preparations

This study was approved by the Animal Care and Use Committee of the Taipei Medical University. Twenty-six pathogen-free adult male Sprague Dawley rats weighing 250 to 300 g were maintained on a 12-hour light–dark cycle with free access to food and water. Animals were anesthetized using intraperitoneal injection of pentobarbital sodium (50 mg/kg; Abbott, North Chicago, IL), weighed, and placed supine on a heating pad. A polyethylene catheter (PE-50, Becton Dickinson, Sparks, MD) containing heparinized isotonic saline was inserted into one carotid artery to sample blood for gas analysis. Blood gas tensions were measured using a blood gas analyzer (model 1620, Instrumentation Laboratories, Lexington, MA). A tracheostomy was performed, and a 14-gauge plastic cannula was inserted into the trachea. The endotracheal tube was connected to a volume-cycled small animal ventilator (SAR-830/AP, CWE, Ardmore, PA) and all rats were ventilated for 90 minutes at a tidal volume of 40 mL/kg, zero positive end-expiratory pressure, a respiratory rate (RR) of 30 breaths/min, an inspiratory to expiratory time ratio of 1:1, and an inspiratory O_2 fraction of 0.21.

2.2. BCPAP device set-up and measurement of representative airway pressure oscillations

The conventional and high-amplitude BCPAP devices were set up with the expiratory limb at 0° and 135°, respectively (Fig. 1).

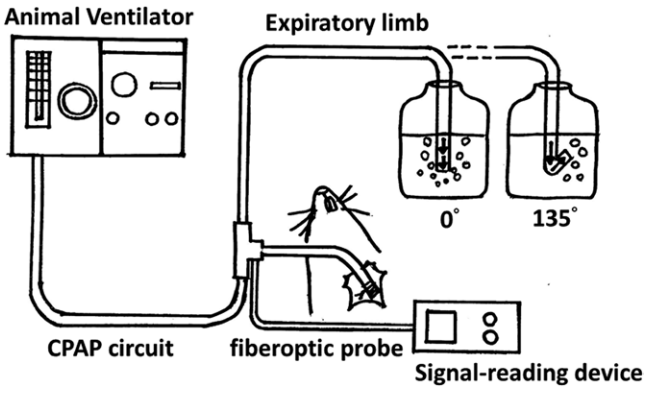

Fig. 1 BCPAP devices with expiratory limbs at two different angles. The angle of the expiratory limb was 0° in the conventional BCPAP device, and the angle of the expiratory limb was 135° in the high-amplitude BCPAP device. All the other settings were identical in both BCPAP devices. BCPAP, bubble continuous positive airway pressure.

Except for the expiratory limb angles, the circuit structures and other settings of both devices were identical. The animal ventilator (model SAR-830/AP, CWE, Ardmore, PA) provided gas flow at a rate of 1 L/min. The expiratory limbs of the two devices were both submerged under 5 cm of water to obtain 5 cmH_2O CPAP. To compare the pressure oscillations produced by the conventional and high-amplitude BCPAP devices in vivo, we assigned one model rat, euthanized immediately after the measurement, to undergo the VILI process described earlier and then alternately to receive conventional BCPAP and high-amplitude BCPAP for 3 seconds. The airway pressure oscillations for the model rat produced by these two BCPAP devices were measured using a fiberoptic probe (OpSens Technologies, Quebec, Canada). The tip of the sensor was positioned at the distal port of the open channel. The proximal end of the micropressure sensor cable was connected to a signal-reading device (LifeSens, OpSens, Canada; Fig. 1). Data were acquired using a digitizer (iWorx 404) connected to a computer.

2.3. Experimental protocol

After 90 minutes of high tidal volume ventilation, arterial blood gases were assessed and the rats were randomized into four groups: a control group in which the animals were euthanized immediately (n = 3), a group that received SB treatment (n = 8), and two BCPAP groups that were treated with the bubble technique using an expiratory limb angled at either 0° (BCPAP 0; n = 8) or 135° (BCPAP 135; n = 7) for 90 minutes. During the experiment, anesthesia was maintained through intraperitoneal injection of pentobarbital sodium (50 mg/kg). The depth of the underwater seal in the BCPAP circuits was adjusted to 5 cm. RRs and arterial blood gas levels were measured at 0, 30, 60, and 90 minutes after BCPAP treatment.

2.4. Lung processing and pressure–volume curve measurements

Control rats were killed immediately after 90 minutes of high tidal volume ventilation. Rats in the SB and BCPAP groups were killed 90 minutes after SB or BCPAP intervention, and the tracheal tube was clamped for 3 minutes to facilitate oxygen absorption and lung collapse. A static deflation pressure–volume curve was obtained by inflating the lungs with air to a 25-cmH2O pressure for 1 minute and recording the maximal lung volume. The pressure was then progressively decreased and held for 30 seconds at 20-, 15-, 10-, 5-, and 0-cmH2O with lung volume measured at each pressure. The measured volumes at all pressures were recorded and corrected for the compression volumes of the system and expressed as milliliter per kilogram of body weight. After completing the static pressure–volume curve measurements, the thorax was opened and the lung was removed. Right lung tissues were used for histologic examination. Three repeated saline lavages of the left lung were combined for the bronchoalveolar lavage fluid (BALF) analysis and the aliquots were saved for further analysis.

2.5. BALF protein and cytokines analysis

Total BALF protein concentration, a lung injury marker, was measured with a protein assay kit (BioRad Laboratories, Richmond, CA, USA) according to the Bradford method, by using bovine serum albumin as the standard. Interleukin-6 (IL-6), macrophage inflammatory protein-2 (MIP-2), and tumor necrosis factor-α (TNF-α) levels in the BALF were determined using an enzyme-linked immunosorbent assay (ELISA) kit (Cloud-Clone Corp., Houston, TX, USA) and a rat-specific ELISA kit (KRC1022, Invitrogen Life Technologies, Carlsbad, CA, USA). The data were expressed in picogram per milliliter.

2.6. Histologic examination

Lung tissue was removed and placed in a fixative for 48 hours at room temperature. After serial dehydration in alcohol, the tissues were embedded in paraffin. After deparaffinization in

xylene, 5-μm-thick tissue sections were rehydrated in decreasing ethanol concentrations. Hematoxylin and eosin staining was performed for general histological observation. All sections were viewed and photographed using a Nikon Eclipse E600.

2.7. Statistical analysis

The results are presented as means ± SEM. The analysis was performed using SPSS (version 17.0; SPSS, Inc., Chicago, IL, USA). Statistically significant differences were analyzed using the Kruskal–Wallis test. Between-group comparisons were performed using the Mann–Whitney *U* test. Significance was accepted at $p < 0.05$.

3. RESULTS

3.1. Measurement of representative airway pressure oscillations

The airway pressure oscillations measured in the model rat lung are depicted in Figure 2. The mean airway pressures of the model rat lung while receiving conventional BCPAP or high-amplitude BCPAP were comparable (5.08 and 5.35 cmH_2O, respectively), but the amplitudes of pressure oscillations measured during high-amplitude BCPAP treatment were greater than those measured during conventional BCPAP treatment (0.96 vs 0.70 cmH_2O).

3.2. Time course of changes of arterial blood gas values

Comparisons of pH, PaO_2, $PaCO_2$, and RR from the start of high tidal volume ventilation to the end of BCPAP support between the BCPAP (BCPAP 0 + BCPAP 135) group and SB group are presented in Figure 3A–D. The baseline arterial blood gas levels were comparable in the BCPAP and SB groups. The BCPAP group exhibited significantly lower pH at 120 minutes than did the SB group (Fig. 3A). The BCPAP group exhibited comparable PaO_2 values and RRs (Fig. 3B, D) but significantly higher $PaCO_2$ values (Fig. 3C) at 120 and 180 minutes than did the SB group. Moreover, both BCPAP groups exhibited comparable arterial blood gas levels (Fig. 4A–C); however, the BCPAP 135 group had lower but nonsignificant RRs than did the BCPAP 0 group (Fig. 4D).

3.3. BALF protein and cytokines

The BCPAP 135 group had significantly lower BALF protein levels than did the SB group. The BCPAP 0 group demonstrated a trend of lower BALF protein levels compared with the SB group. The BCPAP 135 group demonstrated nonsignificantly lower BALF protein levels than did the BCPAP 0 group (Fig. 5A). The BCPAP 135 group had significantly lower IL-6 levels than did the SB and BCPAP 0 groups. The BCPAP 0 group had nonsignificantly lower IL-6 levels than did the control group (Fig. 5B). Both BCPAP groups exhibited nonsignificantly lower BALF MIP-2 levels than did the SB group; the SB group had significantly higher MIP2 levels than did the control group (Fig. 5C). No statistically significant difference or a trend of difference with respect to TNF-α levels was noted among the control, SB, BCPAP 0, and BCPAP 135 groups (Fig. 5D).

3.4. Pressure–volume curve

The control group had significantly higher lung volume than did the BCPAP 135 group at 0-cmH_2O lung pressure; the control group had significantly higher lung volume than did the BCPAP (BCPAP 0 + BCPAP 135) group at 5- and 10-cmH_2O lung pressure. The SB group had significantly higher lung volume than did the BCPAP 135 group at 20-cmH_2O lung pressure. The BCPAP 135 group had nonsignificantly lower lung volume than did the BCPAP 0 group (Fig. 6A).

3.5. Lung histology

The representative lung histology images of four groups are depicted in Figure 6B. The control group exhibited the most hyperextended alveolar status, and the BCPAP 135 group exhibited the most homogeneously recruited alveolar status.

4. DISCUSSION

The meta-analysis of Fischer and Buhrer included trials comparing CPAP with mechanical ventilation with or without a prophylactic surfactant, trials that compared CPAP with INSURE (INtubate, SURfactant, Extubate), and trials that evaluated less invasive methods of administering a surfactant. The authors concluded that the odds ratio for death or BPD was 0.83 (95% CI, 0.71-0.96) with strategies aimed at avoiding intubation outperforming others.[21] The cohort study by Narendran et al. compared BCPAP and conventional CPAP for managing respiratory distress syndrome in preterm babies and reported a significant reduction in postnatal steroid use when BCPAP was used and a decreasing trend for the incidence of chronic lung disease when BCPAP was used.[22] In an observational study from Canada, Pelligra et al. compared ventilator-derived CPAP and BCPAP according to an analysis of the treatment of 821 babies < 32-weeks-old and discovered that BCPAP use significantly reduced exogenous surfactant and postnatal steroid use

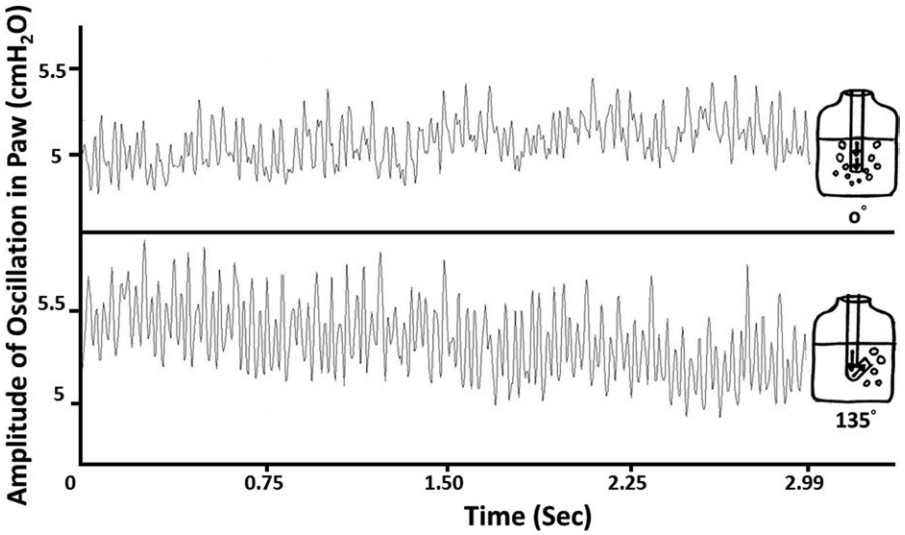

Fig. 2 Airway pressure oscillations of the model rat lung while receiving conventional BCPAP (BCPAP with an expiratory limb at 0º) or high-amplitude BCPAP (BCPAP with the expiratory limb at 135º). BCPAP, bubble continuous positive airway pressure; Paw, airway pressure.

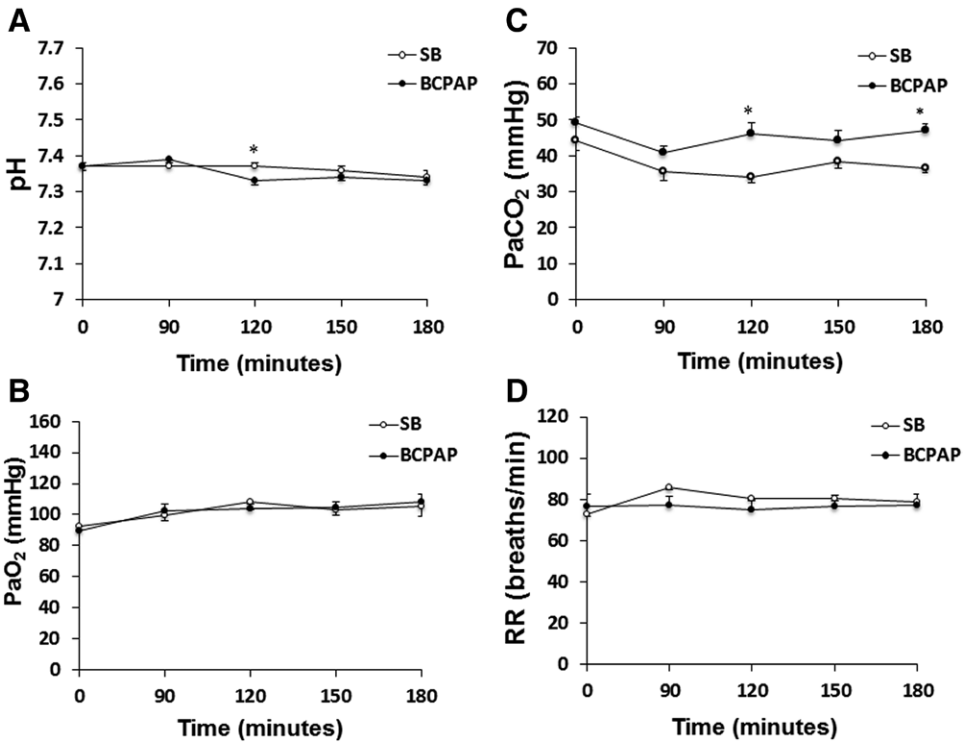

Fig. 3 Time course of changes of arterial blood gas values during the experiment. Comparison of the time courses of changes of arterial blood gas values between the BCPAP and SB groups (A–D). Time 0 denotes the start of high tidal volume ventilation. Time 90 denotes the start of BCPAP or SB (*$p < 0.05$ denotes statistical significance compared with the control group at each time point). Means ± SE of SB, BCPAP, and BCPAP with various expiratory limb angles are depicted. BCPAP, bubble continuous positive airway pressure; SB, spontaneous breathing; RR, respiratory rate.

and mechanical ventilation duration.[23] This lung protective effect of BCPAP is compatible with our previous work;[16] it may partially explain the reason that preterm babies receiving CPAP had a lower BPD incidence compared with mechanically ventilated babies. The findings that the BCPAP group had a trend of lower BPD incidence and demonstrated a significant reduction

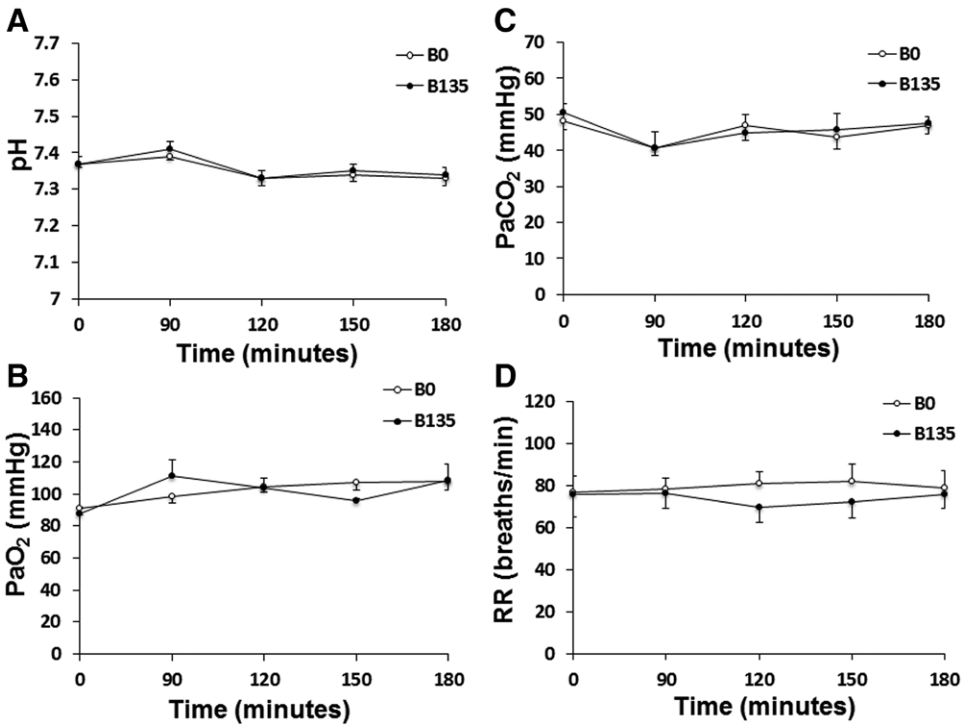

Fig. 4 Comparison of time courses of changes of arterial blood gas values between BCPAP groups with expiratory limbs at 0° and 135° (A–D). Time 0 denotes the start of high tidal volume ventilation. Time 90 denotes the start of BCPAP or SB (*$p < 0.05$ denotes statistical significance compared with the control group at each time point). Means ± SE of SB, BCPAP, and BCPAP with various expiratory limb angles are presented. BCPAP, bubble continuous positive airway pressure; RR, respiratory rate; SB, spontaneous breathing.

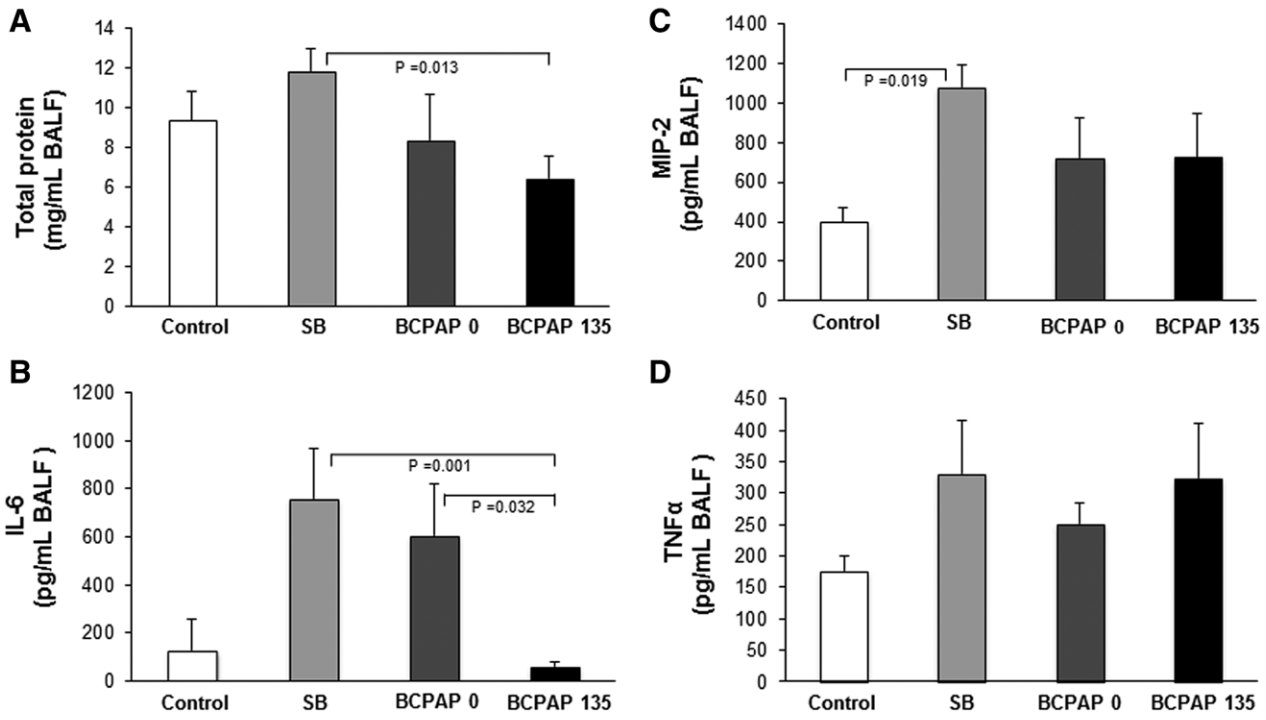

Fig. 5 BALF analysis in control, SB, and BCPAP groups. A, BALF total protein; B, IL-6; C, MIP-2; and D, TNF-α concentrations. Means ± SE of n = 4 independent experiments are displayed. BALF, bronchoalveolar lavage fluid; BCPAP, bubble continuous positive airway pressure; IL-6, interleukin 6; MIP-2, macrophage inflammatory protein 2; SB, spontaneous breathing; TNF-α, tumor necrosis factor-α.

in exogenous surfactant and postnatal steroid use and mechanical ventilation duration from the aforementioned clinical studies indicated that BCPAP may provide a superior lung protective effect and more homogenous alveolar recruitment than would conventional CPAP. These clinical findings are supported by a study of an ovine model of preterm lung disease performed by Pillow et al., which determined that the BCPAP group had lower alveolar protein levels than did a conventional CPAP group.[15] This study did not compare BCPAP with conventional CPAP directly but compared two different amplitudes of BCPAP and determined that only the BCPAP 135 group had significantly lower alveolar protein levels than did the SB group and the BCPAP 135 group had significantly lower BALF IL-6 levels than the BCPAP 0 group, indicating that high-amplitude BCPAP potentially provides a lung protective effect superior to that of conventional BCPAP.

No significant differences with respect to TNF-α and MIP-2 levels were evident among the SB, BCPAP 0, and BCPAP 135 groups; however, average TNF-α and MIP-2 levels in the BCPAP (BCPAP 0 + BCPAP 135) group were lower than those in the SB group. IL-6 is probably the most sensitive cytokine marker in this rat model of VILI, and further study with a larger number of experimental rats might be warranted to clarify the roles of TNF-α and MIP-2 in this model of acute lung injury.

The main feature of BCPAP that differs from constant-pressure CPAP is the stochastic resonance phenomenon. The key feature of stochastic resonance is that the optimal amplitude has the best lung volume recruitment effect.[17] Diblasi et al. used BCPAP with various amplitudes and determined that high-amplitude BCPAP provides more respiratory support and requires less breathing effort than does conventional BCPAP in lavaged juvenile rabbits.[20] In this study, we demonstrated that high-amplitude BCPAP produced using an expiratory limb at 135° had a superior lung protective effect than did conventional BCPAP (ie, BCPAP 135 group had significantly lower alveolar protein than the SB group and significantly lower BALF IL-6 levels than the BCPAP 0 group). Moreover, the SB group exhibited significantly higher MIP-2 levels than the control group; however, the arterial blood gas concentrations and RRs were similar to the BCPAP group, indicating an ongoing but hidden inflammatory process in the SB group.

Theoretically, the BCPAP group should have higher PaO_2, lower $PaCO_2$, and higher pH of arterial blood gas than the SB group. However, in this study, we failed to demonstrate that the BCPAP group had superior oxygenation to the SB group, and we speculate this is attributable to the relatively good lung compliance in our VILI setting compared with the previous models using lavaged lung. Rather than lower $PaCO_2$ and higher pH, the BCPAP group had higher $PaCO_2$ and lower pH than did the SB group. We speculate that this was because the CPAP level (5 cmH_2O) applied to the BCPAP group was too high, leading to the increased $PaCO_2$ level.[24]

Alveolar overdistension and cyclic atelectasis are the principal initiators of alveolar injury during the VILI process.[25] The pressure–volume curve in this study indicated that the control group had the highest lung volume throughout the lung deflation process among the four groups and most significantly at 0- and 5-cmH_2O lung pressure, suggesting an alveolar overdistended status after mechanical ventilation and a pronounced air trapping phenomenon at the end of the deflation process in the control group. The BCPAP (BCPAP 0 + BCPAP 135) group exhibited significantly lower lung volume than did the control group at 5- and 10-cm H_2O lung pressure, and the BCPAP 135 group exhibited significantly lower lung volume than the control group at 0-cmH_2O lung pressure, indicating that BCPAP treatment after stopping mechanical ventilation could decrease alveolar overdistension caused by the VILI process. Compared with the BCPAP 0 group, the effect of decreasing alveolar overdistension status after VILI might be superior in the BCPAP 135 group because only the BCPAP 135 group had a significantly lower lung volume than did the SB group at 20-cmH_2O lung pressure. Although the difference was nonsignificant, the mean lung volume of the BCPAP 135 group was always lower than that of the BCPAP 0 group throughout the lung deflation process, suggesting that compared with the BCPAP 0 group the BCPAP 135

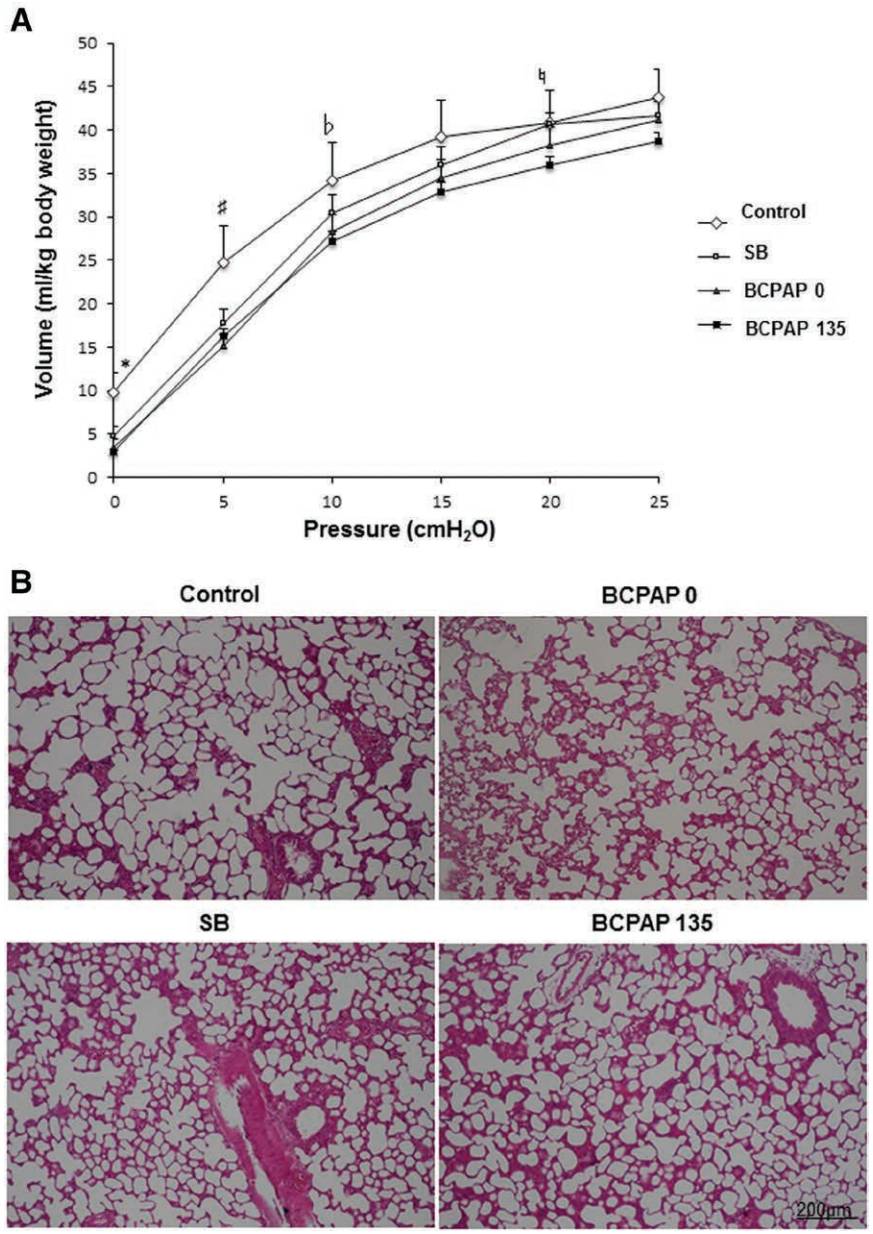

Fig. 6 Pressure–volume curves and representative lung histology images of the control, SB, and BCPAP groups. A, Pressure–volume curves; and B, representative lung histology images of the control, SB, BCPAP 0, and BCPAP 135 groups. Hematoxylin and eosin staining was performed for general histological observation. The microscope magnified the object one hundred times. ($^{*}p < 0.05$ denotes statistical significance with respect to the BCPAP 135 group compared with the control group, $^{\#}p < 0.05$ denotes statistical significance with respect to the BCPAP group (combined BCPAP 0 and BCPAP 135) compared with the control group, $^{\flat}p < 0.05$ denotes statistical significance with respect to the BCPAP group (combined BCPAP 0 and BCPAP 135) compared with the control group, $^{\natural}p < 0.05$ denotes statistical significance with respect to the BCPAP 135 group compared with the SB group at each lung pressure point). Means ± SE of SB, BCPAP, and BCPAP with various expiratory limb angles are presented. BCPAP, bubble continuous positive airway pressure; SB, spontaneous breathing; BCPAP 135, BCPAP with an expiratory limb at 135°; BCPAP 0, BCPAP with an expiratory limb at 0°.

group had less alveolar overdistension status. This phenomenon was compatible with the lung histology findings that the BCPAP 135 group had a mostly homogenous alveolar size and the control group had the most heterogeneous alveolar size among the four groups.

The pilot human study of using BCPAP with the expiratory limb at various angles conducted by Welty et al. discovered that on average the force per breath was lower with Seattle PAP (Seattle bubble NCPAP:BCPAP with the expiratory limb at 135°), indicating less breathing effort among babies who received Seattle PAP than babies who received standard BCPAP (BCPAP with the expiratory limb at 0°).[26] This encouraging finding supports the proposition of using BCPAP with expiratory limbs at different angles.

Whether the low effort of breathing observed using Seattle PAP leads to superior clinical outcomes requires further study; however, our animal study generated high-quality preclinical evidence that using high-amplitude BCPAP may achieve a superior lung protective effect than did conventional BCPAP in the postextubation stage of respiratory diseases.

The limitation of this study is that we used adult rats rather than newborn rats. Kuebler et al. demonstrated that circumferential stretch activates nitric oxide production in pulmonary endothelial cells through a signaling cascade involving phosphatidylinositol 3-kinase, protein kinase B, and nitric oxide synthase 3 in intact and isolated perfused mouse lung.[27] We speculated that the biochemical and genetic responses of pulmonary endothelial cells to mechanical stretching may be similar in

adult and newborn rat lungs; however, considering the vulnerable characteristic of a newborn lung, the degree of lung injury attributable to pathological overdistension is potentially more severe in newborn lung than in an adult lung.

In conclusion, high-amplitude BCPAP reduced lung inflammation and alveolar overdistension in rats with VILI after mechanical ventilation was terminated. Thus, high-amplitude BCPAP may achieve a lung protective effect superior to conventional BCPAP. This finding indicated the necessity of further research on the short- and long-term effects of high-amplitude BCPAP in the postextubation stage of neonatal respiratory diseases.

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