ORIGINAL ARTICLE

Comparison between Bubble CPAP and Ventilator-derived CPAP in Rabbits

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Background: Continuous positive airway pressure (CPAP) is used in infants with respiratory distress and apnea. Bubble CPAP (B-CPAP) and ventilator-derived CPAP (V-CPAP) are two of the most popular CPAP modes, and use different pressure sources. However, few studies have been performed to compare their differences and effectiveness. This study was to determine whether B-CPAP and V-CPAP would have different effects on vital signs and arterial blood gas analysis.
Methods: We performed a randomized crossover study to measure vital signs, including mean blood pressure (MBP), heart rate (HR), and respiratory rate (RR), in 12 ketamine-anesthetized healthy rabbits receiving endotracheal intubation by tracheostomy with B-CPAP or V-CPAP. Arterial blood was also sampled and analyzed for PaO_2, $PaCO_2$, HCO_3^- and pH.
Results: We observed statistically significant decreases in RR, pH and PaO_2 with corresponding incrases in $PaCO_2$ and HCO_3^- during the V-CPAP; however, no significant changes from baseline were observed for B-CPAP. Neither modality resulted in statistically significant changes in MBP or HR. Both forms of CPAP altered vital signs and arterial blood gases in a similar manner. There was a trend towards a lower percentage of change from baseline in all variables in B-CPAP compared with V-CPAP.
Conclusions: Our results suggest that B-CPAP seems to be superior to V-CPAP in terms of its effect on arterial blood gases and vital signs. We speculate that B-CPAP could have certain protective effects that better preserve both arterial blood gases and vital signs when compared to V-CPAP. However, the results of this study still need to be tested by clinical study.

1. Introduction

Continuous positive airway pressure (CPAP) was first used to support the breathing of neonates in the early 1970s.[1] Neonatal applications of CPAP include the prevention of extubation failure[2] and the apnea of prematurity,[3] and offers an alternative to intubation and ventilation in respiratory distress syndrome.[4] There are several techniques for CPAP generation; however, little evidence exists demonstrating the superiority of one technique over another.[5−7]

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For the past 30 years, CPAP has been primarily delivered to neonates using certain devices connected to a conventional mechanical ventilator (ventilator-derived CPAP, V-CPAP). In V-CPAP, a variable resistance in a valve is adjusted to provide resistance to the flow of air. Underwater bubble CPAP (B-CPAP) has provided an alternative to pressure derived from conventional ventilators and has remained in use since first devised in the early 1970s.[1] The positive pressure in the circuit is achieved by simply immersing the distal expiratory tubing in a water column to a desired depth rather than using a variable resistor. Although these two different pressure sources for CPAP delivery have been used for three decades, surprisingly few studies have been performed to compare their differences and effectiveness.[8,9]

The objective of this study was to determine whether vital signs and arterial blood gas analyses were influenced by the application of CPAP in spontaneously breathing healthy rabbits, and if there were an impact, whether B-CPAP and V-CPAP would differ in this regard.

2. Materials and Methods

The experiments were approved by the local animal ethics committee of the National Defense Medical Center. Twelve pathogen-free, female, juvenile New Zealand White rabbits (mean body weight 1.86 ± 0.22 kg) were used in this study.

2.1. Surgical preparation

Animals were anesthetized by means of an intramuscular injection of a mixture of ketamine (23 mg/kg), acepromazine (0.58 mg/kg), and xylazine (0.8 mg/kg). The left marginal ear vein was cannulated to administer a continuous infusion of 5% dextrose at a rate of 5 mL/kg/h, and a catheter was inserted in the right auricular artery to obtain samples for blood gas analysis. The animals were placed in the supine position and given a tracheotomy just below the cricoid cartilage. An endotracheal tube of 3.0 mm inner diameter was then inserted. The tracheal walls were tightened with 3–0 nylon suture around the endotracheal tube to avoid accidental extubation and leakage of air.

The endotracheal tube was connected to a ventilator (Sechrist Infant Ventilator, model IV-100B, Sechrist Industries, Anaheim, CA, USA), and the rabbits were allowed to breathe spontaneously without assisted ventilation (ventilation rate = 0, FiO_2 = 21%, flow = 8 L/min). The end of the exhalation hose was open to make the circuit at a CPAP of 0 cmH$_2$O. A catheter primed with normal saline containing heparin was introduced into the left carotid artery
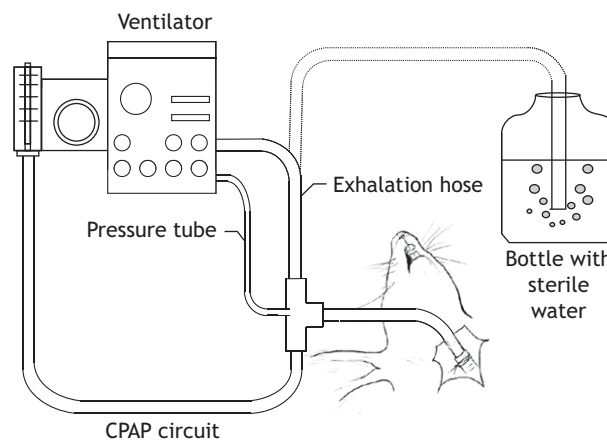
Figure 1 Schematic representation of the CPAP circuit. For V-CPAP, the exhalation hose was connected to the exhalation valve of the ventilator; for B-CPAP, the exhalation hose was submerged under 5 cm of water.

for the continuous registration of arterial blood pressure and heart rate (PowerLab hardware, Chart version 4.2 software; AD Instruments, Castle Hill, Australia).

2.2. CPAP setup

CPAP was achieved by using two modes: V-CPAP and B-CPAP. The circuit structures for both modes were almost identical. The ventilator (Sechrist Industries) provided gas flow at a rate of 8 L/min. The only difference between the modes was the site to which the end of the exhalation hose connected. For V-CPAP, the hose was connected to the exhalation valve of the ventilator. The pressure tube was connected to the Y-piece and the pressure was adjusted at 5 cmH$_2$O. For B-CPAP, the hose was submerged under 5 cm of water to obtain 5 cmH$_2$O of CPAP (Figure 1).

2.3. Anesthesia maintenance

During the surgical preparation, anesthesia was maintained with repeated intravenous injections of ketamine (20 mg/kg). After instrumentation, the rabbits received another dose of ketamine to prevent them from awakening during the experiment. The injection of ketamine decreased the animals' blood pressure and heart rate, though the measures returned to baseline, usually within 5 minutes. In all animals, we allowed a delay of at least 10 minutes after the injection of ketamine and before experimentation to obtain stable circulatory conditions.

2.4. Experimental protocol

In a crossover design, each rabbit received two courses (I, II) of the experimental procedure (Figure 2). Each
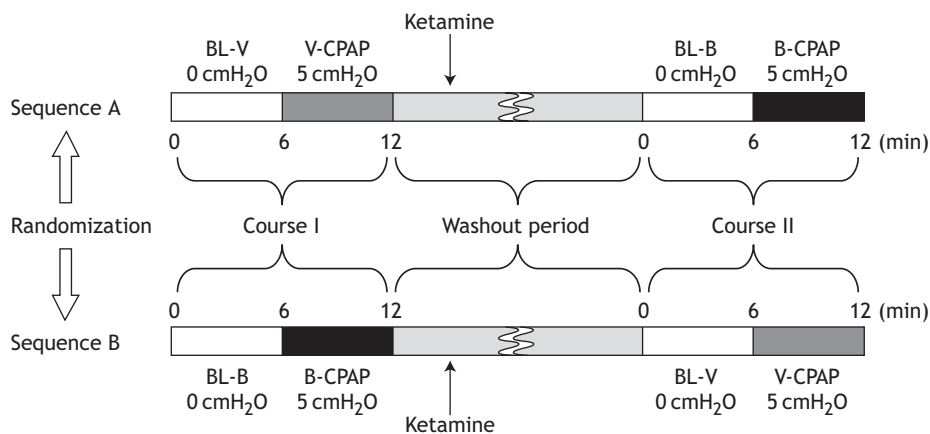
Figure 2 Study protocol. Each rabbit was randomly assigned to one of two sequences—A or B. BL=baseline period.

course was comprised of two 6-minute periods. In the first period, which was a baseline period (BL-V in sequence A; BL-B in sequence B), the rabbits received $0\,cmH_2O$ of CPAP by keeping the exhalation hose open. In the second period, the rabbits were randomly assigned to receive V-CPAP (sequence A) or B-CPAP (sequence B) by connecting the end of the exhalation hose to the exhalation valve of the ventilator or submerging it into water. Randomization was performed using a computer program that generated random numbers to determine the mode of CPAP to be first used.

After completing course I of the experiment, CPAP was returned to $0\,cmH_2O$ by disconnecting the exhalation hose from the ventilator (in sequence A) or pulling it out of the water (in sequence B). The rabbits then received another dose of ketamine, and a second course was performed at least 10 minutes later when the rabbits' circulatory conditions were stable. In the first period of course II, the CPAP mode was still $0\,cmH_2O$ as a baseline (BL-B in sequence A; BL-V in sequence B). In the second period of course II, the CPAP mode was changed to the CPAP mode not used in the second period of course I.

2.5. Data collection

Vital signs data, including mean blood pressure (MBP), heart rate (HR) and respiratory rate (RR), were collected during the 2.5- to 4.5-minute timeframe of each period, and were used for statistical analysis. RR was measured by a manual count of chest movements over this 120-second timeframe. The mean of each variable was used to represent the result for the period.

Arterial blood was sampled for blood gas analysis at 5 minutes into each period. Arterial blood samples were analyzed for PaO_2, $PaCO_2$, HCO_3^-, and pH by a blood gas analyzer (ABL 510, Radiometer, Copenhagen, Denmark).

2.6. Statistical analysis

The Wilcoxon signed ranks test was used for comparisons of vital signs (MBP, HR and RR) and arterial blood gas (PaO_2, $PaCO_2$, HCO_3^- and pH) between periods (BL-V and V-CPAP, BL-B and B-CPAP, and BL-V and BL-B) and between the percentage change from baseline of each CPAP modality. To test for "carry-over" and "period" effects, we used nonparametric Mann-Whitney tests (two-tailed) on the sums and the differences, respectively, of these variables for the V-CPAP and B-CPAP. Statistical analysis was performed using SPSS software for Windows, version 11.0 (SPSS, Inc., Chicago, IL, USA). A p-value ≤ 0.05 was considered statistically significant.

3. Results

In total, we performed 24 courses of experiments. Six rabbits were randomly assigned to receive sequence A, and six received sequence B. Accordingly, there were twelve V-CPAP periods and twelve B-CPAP periods in this study.

The effect of the two different modes of CPAP on vital signs (RR, MBP and HR) and arterial blood gas (PaO_2, $PaCO_2$, HCO_3^- and pH) are shown in Figures 3 and 4. When we compared data from the two baseline periods, we found no significant differences except in MBP, which was significantly higher during BL-V than BL-B ($p=0.018$). We observed statistically significant decreases in RR, pH and PaO_2 with corresponding increases in $PaCO_2$ and HCO_3 during the V-CPAP; however, no significant changes from baseline were observed for B-CPAP. Neither modality resulted in statistically significant changes in MBP or HR.
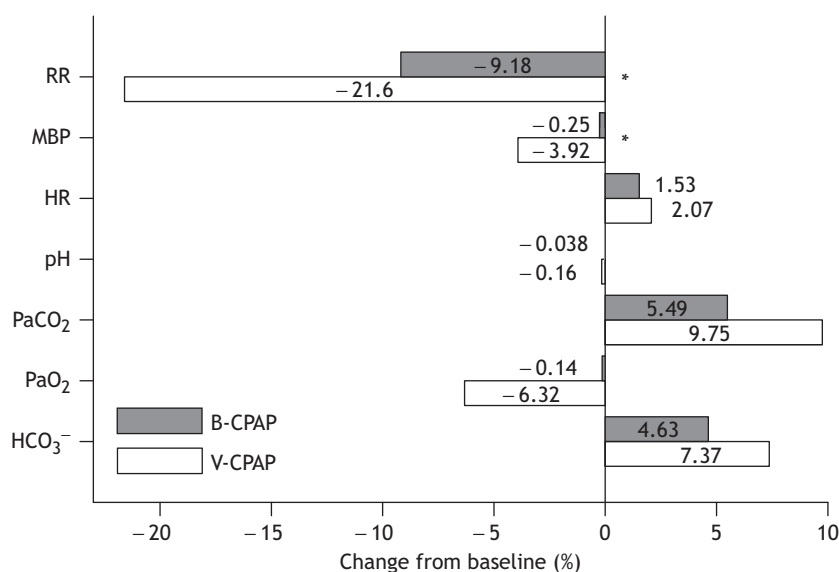
The mean percentage of change in variables from baseline of these two CPAP modalities is shown in Figure 5. Both forms of CPAP altered vital signs and
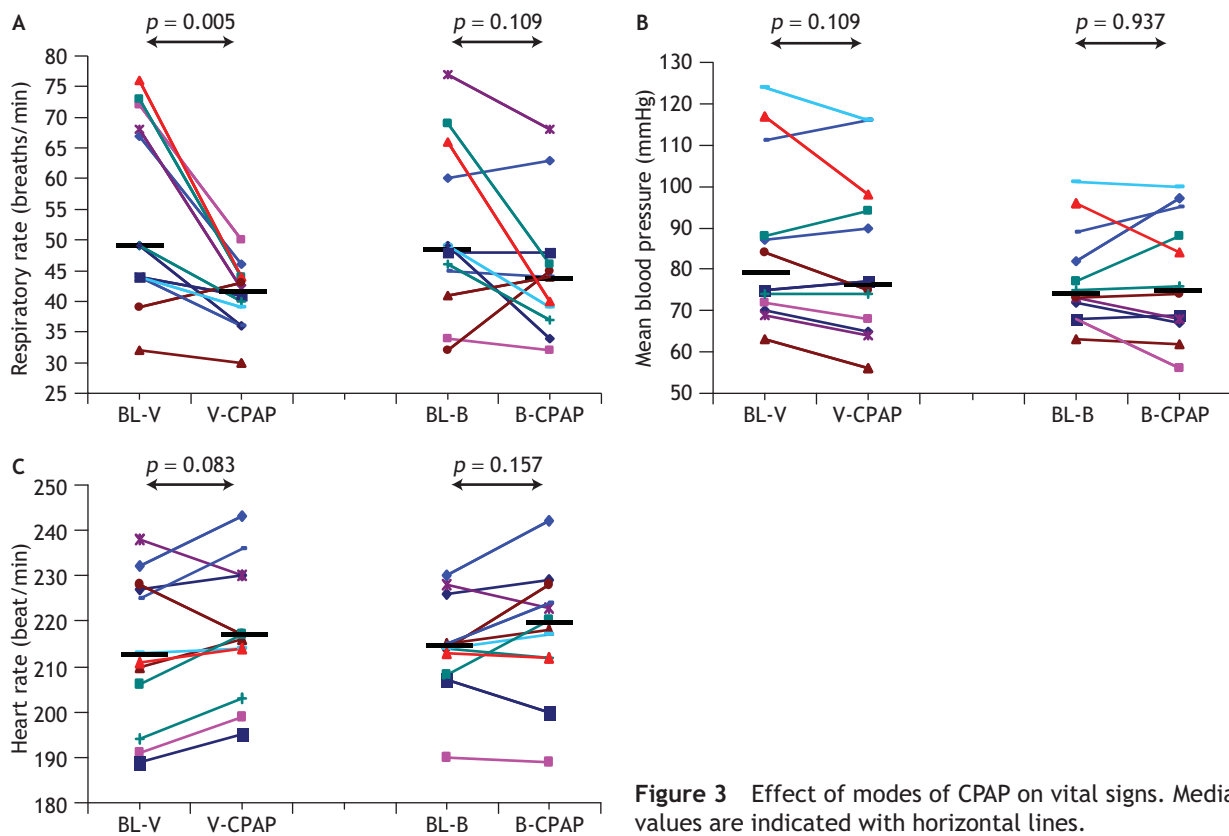
Figure 3 Effect of modes of CPAP on vital signs. Median values are indicated with horizontal lines.
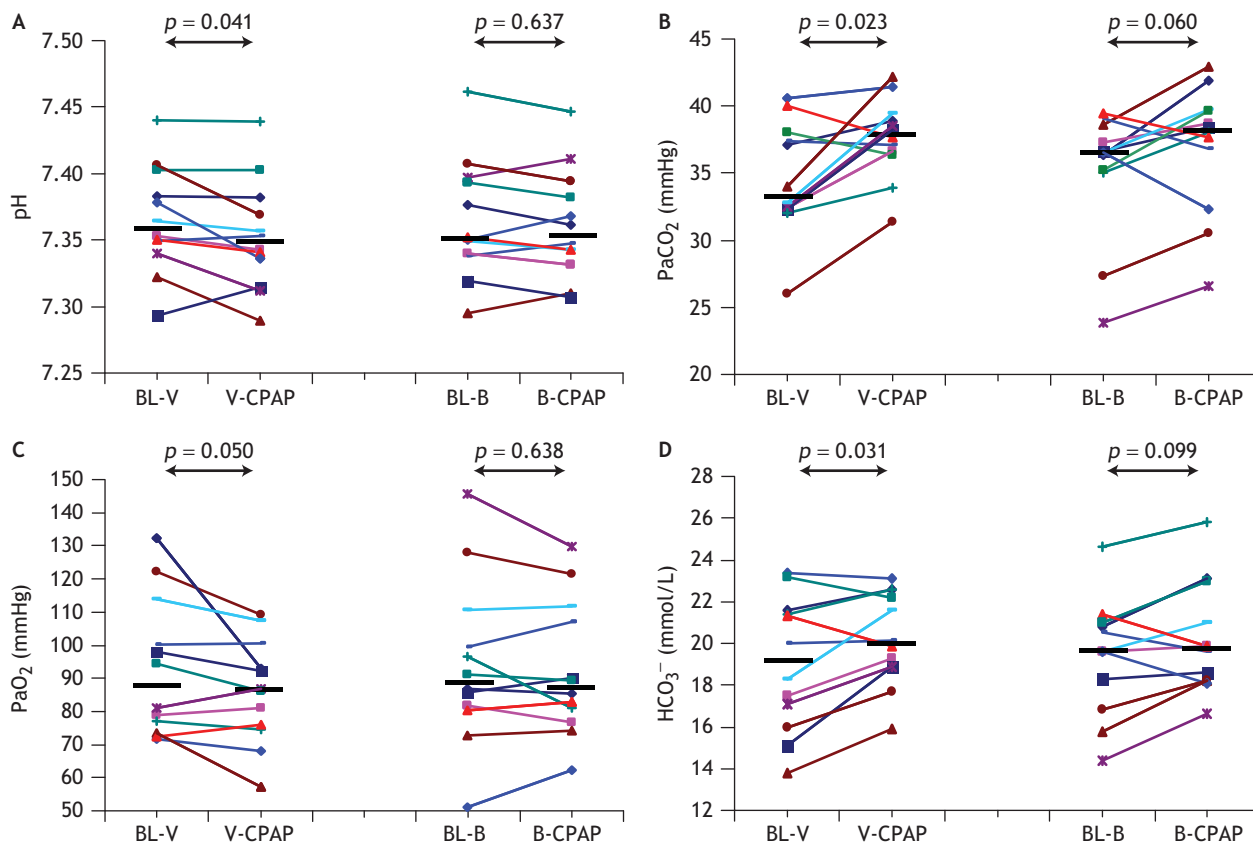
Figure 4 Effect of modes of CPAP on arterial blood gas measures. Median values are indicated with horizontal lines.

Figure 5 Mean percentage change in variables from baseline of each CPAP modality. *=mean percentage change from baseline has reached significance.

arterial blood gases in a similar manner. The changes tended to be higher in all of these variables during V-CPAP than B-CPAP, and the differences between these two CPAP modalities in mean percentage change from baseline in RR and MBP were significant ($p=0.023$ and 0.050, respectively). There were no significant carryover or period effects, except in MBP (carryover effect, $p=0.01$).

4. Discussion

In this study, we demonstrated that V-CPAP and B-CPAP both affected vital signs and arterial blood gases in a similar manner in the healthy rabbit model. Moreover, a striking finding in our study was that B-CPAP had no significant effect on vital signs and arterial blood gases, but V-CPAP significantly influenced both arterial blood gases and the respiratory rate. In addition, B-CPAP had a smaller percentage change from baseline than V-CPAP, although the difference between them was only significant in the respiratory rate and mean blood pressure. These findings suggest that B-CPAP is superior to V-CPAP in terms of its effect on arterial blood gases and vital signs.

B-CPAP, in addition to providing positive airway pressure, delivers mechanical oscillatory vibrations that are transmitted into the chest secondary to the non-uniform flow of gas bubbles across a downstream underwater seal. These vibrations simulate waveforms produced by high-frequency ventilation (HFV).[8,10] Accordingly, B-CPAP may possess the characteristics of CPAP and HFV at the same time, and this may make B-CPAP to different V-CPAP. Hemodynamics has

been reported to be better preserved during HFV than during conventionally controlled mechanical ventilation.[11,12] However, the effect of B-CPAP on circulation is, to our knowledge, untested. Whether or not our results were related to the bubble-associated high-frequency oscillation needs further exploration.

In general, the application of CPAP improves gas exchange, increases PaO_2 and decreases $PaCO_2$ due to increases in functional residual capacity. However, surpassing optimum CPAP levels can result in a fall in tidal volume and a rise in dead space ventilation, leading to a rise in $PaCO_2$. Furthermore, high CPAP levels can lead to a reduction in venous return, compromised cardiac output, increased pulmonary vascular resistance (PVR), and enhanced ventilation-perfusion mismatch, resulting in a lower PaO_2.[13,14] In addition, an increase in PVR results in a shift of the intraventricular septum to the left and inhibits left ventricular filling, further decreasing cardiac output. In our study, the CPAP level we used ($5\,cmH_2O$) may have been too much for healthy rabbit lungs, resulting in a PaO_2 decrease and a $PaCO_2$ increase. Consequently, the cardiac output might have been reduced, producing an insignificantly mild increase in heart rate and a slight decrease in blood pressure.

The decreases in the respiratory rate during CPAP, both ventilator-derived (significant) and bubble (insignificant), are not surprising and have been reported previously. CPAP can assist the respiratory muscles,[15,16] thereby reducing inspiratory work, as indicated by a decrease in the respiratory rate.[17] Furthermore, it has been shown that both inspiratory and expiratory times are increased with CPAP,[18,19] causing a decrease in the respiratory rate.

One of the primary goals in neonatal medicine today is to decrease pulmonary injury and avoid chronic lung disease (CLD) while preserving brain function. Studies have shown that the "Columbia approach"[20,21] in which B-CPAP is used early in the course of respiratory distress in both premature and term-gestation infants, can effectively lower the incidence of CLD.[22–24] At Columbia University, the early initiation of nasal prong B-CPAP in combination with a tolerance to elevated PCO_2 levels has been shown to reduce the incidence of CLD to <5% in infants weighing less than 1500 g.[25]

However, the mode of pressure generation for the delivery of nasal CPAP which most effectively reduces the need for additional respiratory support is still uncertain. It is an issue of significant clinical interest as to whether B-CPAP, as opposed to CPAP only is one of the keys to reducing the incidence of CLD. A comparison of underwater B-CPAP with V-CPAP in preterm neonates suggested that the bubbling contributed to gas exchange which decreases the infant's required work of breathing.[8] The results from that study also suggest that B-CPAP may decrease the need for tidal ventilation, resulting in decreased fatigue and a decreased need for endotracheal intubation and positive pressure ventilation, which may help to reduce the incidence of CLD. Another study compared early B-CPAP with "conventional" (ventilator-derived) CPAP[9] and showed that B-CPAP, but not conventional CPAP, reduced the use of postnatal steroids and produced a directional, but insignificant, decrease in the incidence of CLD. However, this was not a randomized study. Our study showed that B-CPAP had no significant adverse effects on vitals signs and arterial blood gases, but V-CPAP did, which suggests that B-CPAP might have certain protective effects that contribute to a lower incidence of CLD. Further study is needed to investigate these ideas.

There is an important limitation in this study in that we did not measure the actual airway end-distending pressure in either CPAP modality. Courtney et al[26] showed that in three different nasal CPAP devices, there were no significant differences in the respiratory rate and the oxygen changes from baseline among the groups at CPAP of 8, 6, and 4 cmH$_2$O. Coddazzi's study[27] also showed that CPAP increments (from 0 to 10 cmH$_2$O) did not significantly alter PaCO$_2$, respiratory rate, heart rate, or systolic blood pressure. Accordingly, we believe that the failure to demonstrate equivalence between the two modalities with respect to the mean delivered distending pressure may be not so important. Moreover, in current clinical practice, the desired CPAP level is usually achieved just by placing the tubing in a water column to a specific depth in B-CPAP, or adjusting the pressure measured at the Y-piece in V-CPAP, and the actual airway end-distending pressure is usually not measured. We believed that reflecting the true clinical situation was more practical than measuring the actual airway end-distending pressure.

5. Conclusion

In conclusion, from our preliminary results, B-CPAP seems to be superior to V-CPAP in terms of its effect on arterial blood gases and vital signs. We speculate that B-CPAP could have certain protective effects that better preserve arterial blood gases and vital signs than V-CPAP. Because the lungs in the rabbits in our study functioned normally, further study is needed to assess the value of B-CPAP in the treatment of immature lungs or more compromised lung conditions; a larger number of subjects and a longer study duration are also suggested. Since it is always difficult to extrapolate from findings in animal models to humans, the results of this study can only give an indication of what may occur in humans and results still need to be attained by a clinical study.

Acknowledgments

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