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ORIGINAL ARTICLE

Influence of Changing the Diameter of the Bubble Generator Bottle and Expiratory Limb on Bubble CPAP: An *in vitro* Study

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continuous positive airway pressure;
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Background: The noisy component of bubble continuous positive airway pressure (CPAP) is thought to contribute to breathing efficiency and lung volume recruitment, mainly because of stochastic resonance. The magnitude and frequency of the superimposed noise are vital to this process. We wanted to evaluate the *in vitro* effect of changing various parameters of the bubble CPAP circuit regarding the magnitude and frequency of pressure oscillations transmitted to the lung model.
Methods: In a bubble CPAP lung model, we immersed different sizes (3.0 ~ 12.5 mm) of the expiratory limb of the CPAP circuit into different depths under water (2.0 ~ 10.0 cm) and used various diameters (2.9 ~ 9.0 cm) of bubble generator bottles. We also varied the compliance of the model lung. We measured the changes in mean, magnitude, and frequency of pressure oscillations transmitted to the lung model at three different flow rates (namely 4, 8, and 12 L/minute).
Results: Increasing the size and submergence depth of the expiratory limb of a CPAP circuit and decreasing the diameter of the bubble generator bottle intensified the magnitude but diminished the frequency of noise transmitted to the lung model. Decreasing compliance of the lung model intensified both the magnitude and frequency content of pressure oscillations in the model lung.
Conclusion: The size and submergence depth of an expiratory limb of a CPAP circuit, the diameter of the bubble generator bottle, and the compliance of the model lung all influence the magnitude and frequency of the transmitted pressure waveform. Therefore, these factors may affect lung volume recruitment and breathing efficiency in bubble CPAP.

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1. Introduction

For more than 40 years, bubble continuous positive airway pressure (B-CPAP) has been used to treat respiratory distress syndrome in newborn infants during the weaning period or acute stages.[1] The reports by Avery et al[2] and more recently van Marter et al[3] highlighting the low incidence of chronic lung disease in preterm infants at the Columbia Presbyterian Medical Centre, New York, U.S.A have focused attention on the respiratory care practices used by that institution. Specifically, B-CPAP has come into the spotlight. Recently, B-CPAP (Fisher and Paykel HealthCare, Auckland, New Zealand) has also been shown to be associated with a significantly higher rate of successful extubation and reduced duration of continuous positive airway pressure (CPAP) support compared with Infant Flow Driver CPAP (Electro Medical Equipment, Sussex, UK) for infants ventilated for fewer than 14 days.[4] Recently, Pillow et al[5] reported that treatment with B-CPAP immediately after birth enhances gas exchange, lung mechanics, gas mixing efficiency, and lung volume compared with constant-pressure CPAP in an ovine model of preterm lung disease. Although B-CPAP has been used for decades, surprisingly little is known regarding the importance or relevance of the bubble component.

Suki et al[6] suggested that the alveoli and terminal airspaces recruitment process may benefit from the superimposition of noise on the applied driving pressure, exploiting a phenomenon known as stochastic resonance. This feature may be essential for understanding the unique physiological benefits that B-CPAP offers. The principles of stochastic resonance suggest that the amplitude and frequency of superimposed noise can be optimized to achieve the most favorable amplification (i.e., volume recruitment events). Recently, an *in vitro* study reported that the applied bias flow and mechanical properties of the lung influenced the magnitude and the frequency content of the noise transmitted to the lung.[7] In the current study we hypothesized that, in addition to the applied bias flow and compliance of the lung, other factors that would affect the magnitude and frequency of pressure oscillations included the diameter of the bubble generator bottle, and the size and submergence depth of the underwater seal of the expiratory limb of the CPAP circuit. We aimed to evaluate these possible associations in an *in vitro* lung model.

2. Methods

To simulate the respiratory system of a human infant experiencing respiratory disease, we performed experiments in an *in vitro* lung model similar to that used in previous research.[7–9] The lung model incorporated an endotracheal tube (10 cm long, 6.0 mm internal diameter) sealed into the neck of a 2-L glass flask. We created our own experimental B-CPAP system comprising a ventilator-derived flow meter (Sechrist Infant Ventilator, model IV-100B, Sechrist Industries, Anaheim, CA, USA), an inspiratory limb, a connector, expiratory limbs of various sizes, and bubble generator bottles with different diameters (100–2000 mL graduated cylinders). This B-CPAP system was connected to the *in vitro* lung model (Figure 1).

Observations were performed sequentially across a range of 12 different sizes of expiratory limb (3.0–12.5 mm) at nine different depths under water (2.0–10.0 cm) using five different diameters of bubble generator bottles (2.5–9.0 cm) with 10 different model lung compliances, each at three different flows (4, 8, and 12 L/minute, respectively). Lung model compliance was varied by filling the glass flask with different volumes of water (0–1.8 L). When different sizes of expiratory limbs were tested, the depth under the water of the seal was kept constant at 5 cm, the diameter of the bubble generator bottle was constant at 6 cm, and the volume of water

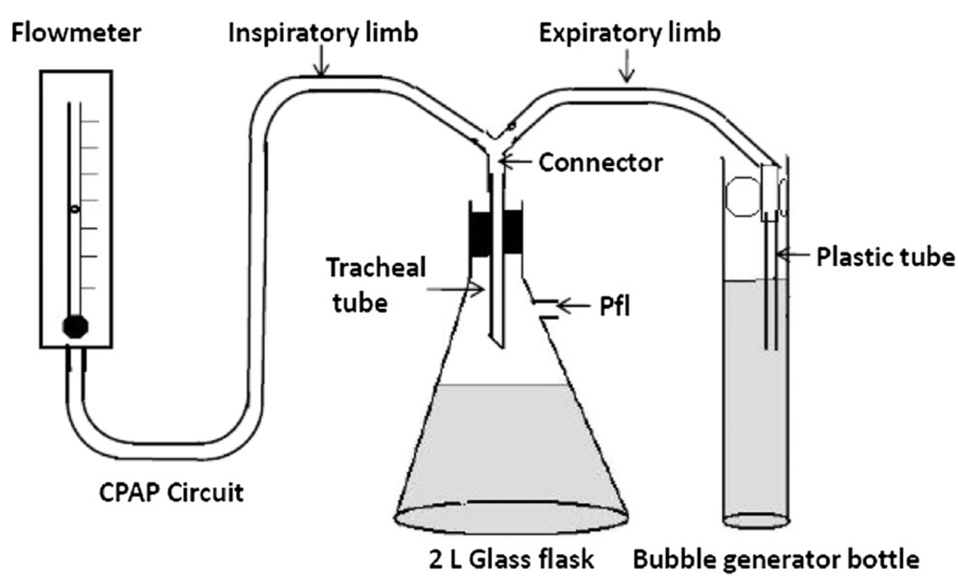

Figure 1 *In vitro* self-styled experimental bubble continuous positive airway pressure system. Lung compliance was adjusted by filling the glass flask with various volumes of water. Plastic tubes with varying diameters were connected to the expiratory opening to adjust the expiratory limb size.

in the glass flask was constant at 1.8 L. When testing the different depths under water of the seal, we kept the size of expiratory limb constant at 10 mm, the diameter of the bubble generator bottle at 6 cm, and the volume of water in the glass flask at 1.8 L. When different diameters of the bubble generator bottle were tested, the size of the expiratory limb was kept constant at 10 mm, the depth under water of the seal at 5 cm, and the volume of water in the glass flask at 1.8 L.

Pressure transducers (PowerLab, AD Instruments, Castle Hill, Australia) were used to measure the pressure within the model lung (Pfl), and they were referenced to atmospheric pressure before we obtained measurements at different settings of the *in vitro* CPAP system. For each measurement, we recorded the pressure oscillations within the model lung for 60 seconds. The recorded signals were filtered (200 Hz), amplified, digitized (PowerLab hardware, Chart version 5.0 software; AD Instruments), and stored on a personal computer for later analysis.

2.1. Analysis

Time-series recordings of the pressure waveforms within the flask (Pfl) were transformed into a frequency domain using power spectral analysis, so that we could assess the extent to which different frequency components were transmitted to the model lung. The mean and magnitude of the pressure waveform within the flask were determined for each of the different settings in the *in vitro* CPAP system. The dominant frequency was defined as the mean frequency of spectral components at which power was greater than or equal to 75 % of maximum power within a measurement period. The effect of the different CPAP settings on the mean, magnitude, and dominant frequency of the pressure waveform within the flask were analyzed by multiple regression tests using SPSS, version 17.0 (SPSS, Inc., Chicago, IL, USA). The level of statistical significance was set at $p < 0.05$.

3. Results

3.1. Effect of expiratory limb size at three different bias flow rates

When the size of the expiratory limb was gradually increased in the experimental CPAP system (from 3.0 to 12.5 mm), the mean measured pressure within the flask (Pfl) and the dominant frequency both gradually decreased ($r^2 = 0.40$, $p = 0.001$; $r^2 = 0.29$, $p = 0.027$, respectively; Figure 2A and C). At the same time, the range of the pressure waveform within the model lung gradually increased ($r^2 = 0.79$, $p < 0.001$; Figure 2B). In addition, an increase in bias flow was related to statistically significant increases in the mean, range, and dominant frequency of the pressure oscillations (all $p < 0.01$; Figure 2). The effect of various bias flow rates on the mean pressure and dominant frequency tended to be more significant for smaller sizes of the expiratory limb (Figure 2A and B). By contrast, the effect of various bias flows on the range of the pressure waveform tended to be more significant for larger sizes of the expiratory limb (Figure 2B).

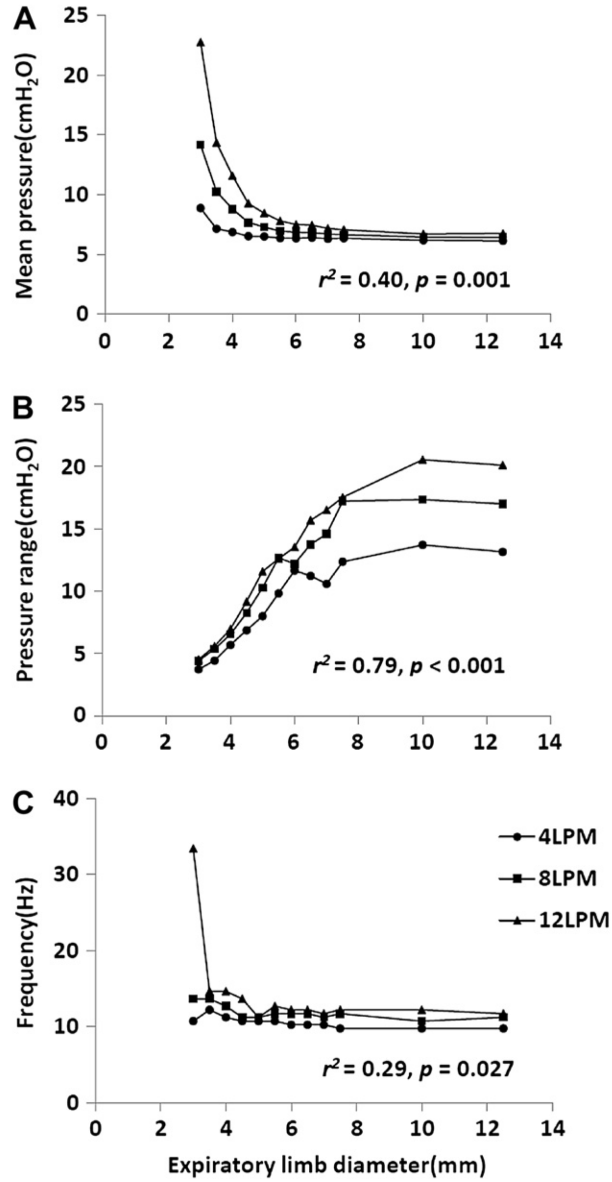

Figure 2 (A) Influence of the expiratory limb diameter on the mean, (B) oscillatory range, and (C) frequency of the transmitted pressure during bubble continuous positive airway pressure.

3.2. Effect of expiratory limb depth at three different bias flow rates

When the depth of the expiratory limb (size 10 mm) was gradually increased from 2 to 10 cm in the experimental CPAP system, gradual and statistically significant increases were noted in the mean measured pressure within the flask (Pfl) and the range of the pressure waveform ($r^2 = 1.00$, $p < 0.001$; $r^2 = 0.87$, $p < 0.001$, respectively; Figure 3A and B). By contrast, the dominant frequency within the model lung gradually decreased ($r^2 = 0.94$, $p < 0.001$; Figure 3C). In addition, an increase in bias flow was significantly related to an increase of the mean, range, and dominant frequency of the pressure waveform, for all tested depths (all $p < 0.001$; Figure 3A—C). However, the effect of

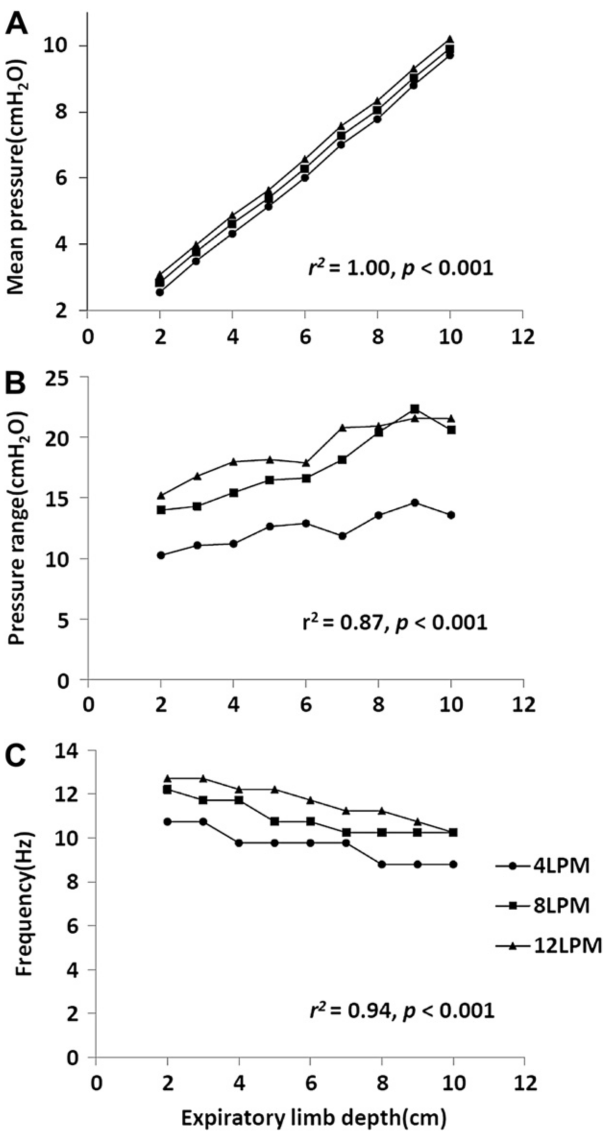

Figure 3 (A) Influence of the submergence depth of the expiratory limb on the mean, (B) oscillatory range, and (C) frequency of the transmitted pressure during bubble continuous positive airway pressure.

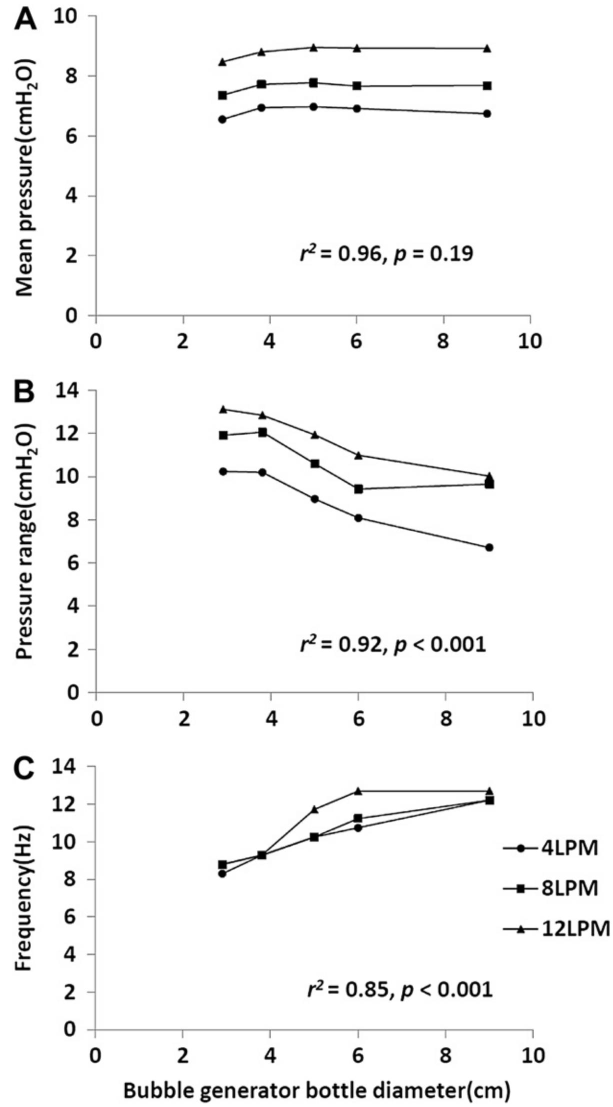

Figure 4 (A) Influence of the diameter of the bubble generator bottle on the mean, (B) oscillatory range , and (C) frequency of the transmitted pressure during bubble continuous positive airway pressure.

different bias flow rates on the mean pressure of the Pfl seemed to be minimal (Figure 3A).

3.3. Effect of diameter of the bubble generator bottles at three different bias flow rates

When we gradually increased the diameter of the bubble generator bottles from 2.9 to 9.0 cm in the experimental CPAP system, the range of the pressure waveform within the model lung gradually decreased, with the relationship being statistically significant ($r^2 = 0.92$, $p < 0.001$; Figure 4B). At the same time, the dominant frequency gradually increased ($r^2 = 0.85$, $p < 0.001$; Figure 4C). However, mean pressure of the pressure waveform was not affected by changing the diameter of the bubble generator bottles ($p = 0.19$; Figure 4A). In addition, an increase in the bias flow was significantly related to an increase in the mean, range, and dominant frequency of the pressure waveforms (all $p < 0.05$; Figure 4A–C).

3.4. Effect of the compliance of the model lung at three different bias flow rates

When the compliance of the model lung was gradually decreased by our filling the flask with various volumes of water ranging from 0 to 1.8 L, statistically significant relationships emerged with the mean, range, and dominant frequency of the pressure waveform, all of which gradually increased as lung compliance decreased (mean: $r^2 = 0.98$, $p < 0.001$; range: $r^2 = 0.88$, $p < 0.001$; dominant frequency: $r^2 = 0.92$, $p < 0.001$; Figure 5A–C). In addition, an increase in bias flow was significantly related to an increase in the mean, range, and dominant frequency of the pressure waveform (all $p < 0.001$; Figure 5A–C).

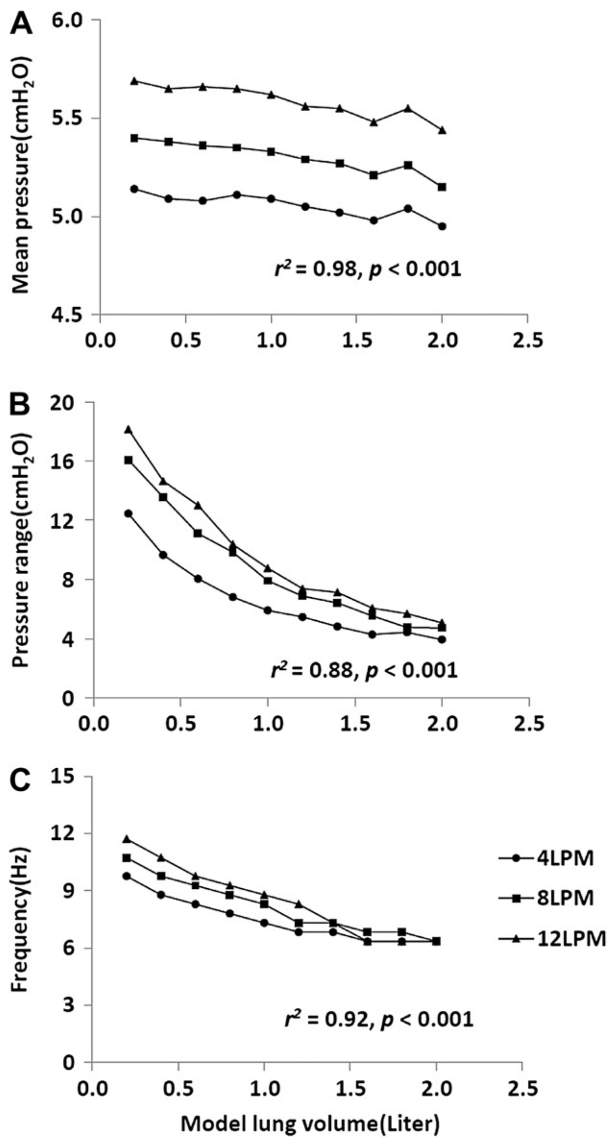

Figure 5 (A) Influence of the model lung compliance on the mean, (B) oscillatory range, and (C) frequency of the transmitted pressure during bubble continuous positive airway pressure.

However, the effect of different bias flow rates on range and dominant frequency of the pressure waveform was more significant when the model lung compliance was lower (Figure 5B and C).

4. Discussion

The promotion of lung volume recruitment under atelectatic conditions and maintenance of existing recruited lung are vital goals of CPAP treatment. Understanding how B-CPAP may affect lung volume allows us to better evaluate whether this technique potentially offers a specific benefit over other CPAP methods.

The main features of B-CPAP that differ from other CPAP methods are the stochastic resonance phenomenon and high frequency oscillator ventilation (HFOV) effect. A key feature of stochastic resonance is that an optimum level of noise exists regarding both amplitude and frequency (bandwidth); within an optimal range, larger amplitudes should have more effect on lung volume recruitment.[6] In addition, similarly to the mechanism of HFOV, larger amplitudes could facilitate a better exchange of gas and efficiency of ventilation, especially carbon dioxide elimination.[7] Pillow et al[7] suggested that the amplitude and frequency composition of the transmitted pressure waveform during B-CPAP would be determined by the mechanical characteristics of the lung, and that amplitude could also be influenced by the amount of bias flow used. The current study found that the size and the submergence depth of an expiratory limb of the CPAP circuit, as well as the diameter of the bubble generator bottle, also influence the magnitude and the frequency of noise transmitted to the model lung. Hence, the same factors might influence the effect of B-CPAP on lung volume recruitment.

When changing the expiratory limb diameter (at three different bias flow rates), we found that, as the expiratory limb diameter increased, the amplitude increased, and the frequency of the transmitted pressure waveform decreased. This finding may be because larger and slower bubbles were generated when the expiratory limb was of a larger size; hence, amplitude was amplified, but frequency was diminished. Interestingly, when the expiratory limb diameter was increased beyond 4.5 mm, any accompanying decrease in frequency seemed to cease to be statistically significant. We thought that this phenomenon might be associated with the low-pass mechanical filtering effect[7,10] in which only pressure waveforms with a specific range of frequency can be transmitted to the model lung under a specific model lung compliance. According to this principle, expiratory limbs of larger sizes might have more effect on lung volume recruitment, especially for low compliance and atelectatic regions of the lung. Regarding the effect of an increased flow on the amplitude and frequency of the transmitted pressure waveform, we observed that higher flow was associated with higher amplitude and frequency, evidently through the effect of bias flow on bubble production. However, the effect on frequency seemed more significant when smaller sizes of expiratory limb were used. Conversely, the effect on amplitude seemed more significant when larger sizes of the expiratory limb were used, especially when we compared the 4 L/minute and the 8 L/minute groups.

When investigating the effect of the submergence depth of the expiratory limb (at three different bias flow rates), we found that the pressure range increased in conjunction with the depth. This might be due to the higher-pressure conditions when bubbles produced, the stronger the resistance they met, and so the higher amplitudes we obtained. In addition, the dominant frequency decreased as the expiratory limb submergence depth increased, which might be due to slower bubble velocity under high-pressure conditions. Hence, greater expiratory limb submergence depth might have more effect on lung volume recruitment. Greater depth can provide higher mean pressure and larger amplitude of pressure oscillation to the atelectatic lung region if the upper limit of the pressure fluctuations lies above the point of the lower inflecture of collapsed lung units on the pressure-volume curve of the respiratory system.[11] We observed that an increased flow was associated with higher amplitude and frequency of the transmitted pressure waveform. When we adjusted the flow rate from 4 to 8 L/minute, the amplitude would significantly increase, but if we adjusted the flow rate from 8 to 12 L/minute, the amplitude increased only slightly. This indicated that moderate flow might be more effective for patients than high flow because the benefit of high flow was only slight, whereas the side effects, such as an increased demand on breathing, might increase significantly.[12]

When changing the bubble generator bottle diameter, we found that as the diameter decreased, the pressure range increased, while the frequency of the pressure waveform decreased. This phenomenon may indicate that the degree of water surface fluctuation may also affect the amplitude and frequency transmitted to the model lung. Higher water surface fluctuation may occur in a smaller bubble generator bottle, under the same settings for the CPAP device, which would result in larger amplitude but lower the frequency of pressure waveform transmitted to the model lung.

Our investigation of the effect of model lung compliance yielded the same findings as those of Pillow et al,[7] namely that as compliance decreased, the amplitude and frequency both increased. The degree of increase in amplitude according to the changes in bias flow tended to be more significant for conditions of poor model lung compliance. To compare the effects of different flow on lung mechanics and gas exchange, Pillow et al[7] used an animal model and two B-CPAP groups; one group received 8 L/minute bias flow, and the other received 12 L/minute. The results suggested no significant physiological benefits when higher flow was used.[5] The reason can be partially explained by our *in vitro* study's finding that there was little effect on amplitude when bias flow rate was adjusted from moderate to high.

4.1. Study limitations

Although an *in vitro* lung model may seem to be a grossly simplified representation of the respiratory system, it has proved useful in the past for investigating aspects of pressure and volume transmission during high-frequency oscillatory ventilation.[8,9,13] Predictions on pressure transmission in the preterm lung have been shown to be reproducible in animal studies.[10,14,15] No leak was incorporated in the *in vitro* lung model; therefore, it is likely that the amplitude of the oscillations transmitted to the model lung were greater than those observed in clinical situations. However, some oscillations are clearly transmitted *in vivo*, with reports of visible chest vibrations when B-CPAP is used in preterm lambs and infants.[16,17]

Due to the problem of air leakage from the bottle plug of the model lung when using a smaller size of endotracheal tube, we chose the 6.0 mm endotracheal tube (ETT) throughout the study, which fitted the bottle plug of the flask most properly. This size of ETT, although larger than the average tracheal size of the neonates and infants using bubble CPAP, does not exceed the upper limit of the size of the trachea for either term or preterm neonates.[18] While the size of the ETT might influence the magnitude and frequency of the noise transmitted to the flask because of the altered flow rate to the bubble generator bottle, it would not, however, alter the relationship between bubble CPAP settings and the transmitted pressure waveform.

4.2. Clinical relevance

No guidelines have yet been established for B-CPAP. In clinical use, the exact device and method often vary according to different hospitals and staff. The current *in vitro* study may thus provide some insight into the clinical application of B-CPAP. First, we suggest using a low to moderate bias flow rate (4–8 L/minute) because our findings indicated that changing bias flow from moderate to high had little effect on the amplitude and frequency of the transmitted pressure waveform. However, the potential harmful effects of high bias flow (such as increased work of breathing) may increase significantly at higher flow rates.

According to our findings regarding expiratory limb size, we suggest using a larger size expiratory limb. This is because larger pressure wave amplitude may have greater effect on lung volume recruitment, resulting in higher gas exchange and ventilation efficiency. The mechanism of stochastic resonance and high frequency oscillatory ventilation are relevant in this regard, especially for babies with low lung compliance. Currently, the most commonly clinical used expiratory limb diameter is approximately 10 mm, and we suggest that larger sizes of expiratory limb may be tried.

According to our findings on the submergence depth of the expiratory limb, increased depth not only increased the mean pressure, but also the pressure range within the model lung. Therefore, we suggest that a greater submergence depth of the expiratory limb should be tried if the patient shows substantially low lung volume or poor compliance.

In addition, smaller sizes of bubble generator bottles should perhaps be considered in clinical use. Our findings revealed that larger amplitude of pressure waveform could be generated under the same B-CPAP setting, using smaller sizes of bubble generator bottle. At present, the most commonly used bubble generator bottle in neonatal intensive care unit in Taiwan is probably the glass intravenous bottle with a diameter of roughly 7 cm. We suggest using a glass-graduated cylinder of 500 ml (5 cm in diameter) to 1000 mL (6 cm in diameter), or other bottles with smaller diameters, such as a feeding bottle. Smaller diameter bottles are especially useful for patients with severe respiratory distress syndrome or other acute respiratory diseases with low lung compliance, where higher amplitude of pressure waveform through CPAP might be helpful.

Finally, our investigations into lung compliance showed that relatively higher amplitude and frequency of the oscillatory pressure waveform were generated under the condition of low model lung compliance. Again, this finding suggests that B-CPAP may be helpful for neonate or preterm infants with acute respiratory disease and low lung compliance, even for extremely small preterm babies. The most unique characteristic of B-CPAP is that it can adjust itself to provide optimal support babies according to their compliance, thereby minimizing the risk of injury.

5. Conclusion

In a closed B-CPAP system, several factors influence the magnitude of the transmitted pressure waveform and may also affect lung volume recruitment. These factors include the size of an expiratory limb, the submergence depth of the underwater seal of the expiratory limb, the diameter of the bubble generator bottle, and the compliance of the model lung. The key factors contributing to the magnitude and frequency of noise appear to be the size and velocity of the bubble, the extent of water surface fluctuation, and water pressure around the bubbles. Consequently, these characteristics are generated by different combinations of sizes and depths of the expiratory limb, different model lung compliance, bias flows, and the diameters of bubble generator bottles. However, by adjusting these variables, it is possible for us to identify the optimal B-CPAP device to offer the best stochastic resonance effect to the sick preterm with weak spontaneous breathing. Further research using *in vivo* models of neonatal respiratory disease is warranted to confirm our findings and their clinical relevance.

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