

Humidity during high-frequency oscillatory ventilation compared to intermittent positive pressure ventilation in extremely preterm neonates: an in-vitro and in-vivo observational study.

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Abstract

Background: Inappropriate humidification of inspired gas during mechanical ventilation can impair lung development in extremely low birthweight (ELBW) infants. Humidification depends on multiple factors, such as the heater-humidifier device used, type of ventilation, and environmental factors. Few studies have examined inspired gas humidification in these infants, especially during high-frequency oscillatory ventilation (HFOV). Our objective was to compare humidity during HFOV and intermittent positive pressure ventilation (IPPV), in vitro and in vivo. **Methods:** In-vitro and in-vivo studies used the same ventilator during both HFOV and IPPV. The bench study used a neonatal test lung and 2 heater-humidifiers with their specific circuits; the in-vivo study prospectively included preterm infants born before 28 weeks of gestation. **Results:** On bench testing, mean absolute (AH) and relative (RH) humidity values were significantly lower during HFOV than IPPV (RH = 79.4% ± 8.1% vs 89.0% ± 6.2%, P<0.001). Regardless of the ventilatory mode, mean relative humidity significantly differed between the 2 heater-humidifiers (89.6% ± 6.7% vs 78.7% ± 6.8%, P=0.003). The in-vivo study included 10 neonates (mean ± SD gestational age: 25.7 ± 0.9 weeks and birth weight: 624.4 ± 96.1 g). Mean relative humidity during HFOV was significantly lower than during IPPV (74.6% ± 5.7% vs 83.0 ± 6.7%, P=0.004). **Conclusion:** Relative humidity was significantly lower during HFOV than IPPV, both in vitro and in vivo. The type of heater-humidifier also influenced humidification. More systematic measurements of humidity of inspired gas, especially during HFOV, should be considered to optimize humidification and consequently lung protection in ELBW infants.

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Abstract

Background: Inappropriate humidification of inspired gas during mechanical ventilation can impair lung development in extremely low birthweight (ELBW) infants. Humidification depends on multiple factors, such as the heater-humidifier device used, type of ventilation, and environmental factors. Few studies have examined inspired gas humidification in these infants, especially during high-frequency oscillatory ventilation (HFOV). Our objective was to compare humidity during HFOV and intermittent positive pressure ventilation (IPPV), in vitro and in vivo.

Methods: In-vitro and in-vivo studies used the same ventilator during both HFOV and IPPV. The bench study used a neonatal test lung and 2 heater-humidifiers with their specific circuits; the in-vivo study prospectively included preterm infants born before 28 weeks of gestation.

Results: On bench testing, mean absolute (AH) and relative (RH) humidity values were significantly lower during HFOV than IPPV (RH = $79.4\% \pm 8.1\%$ vs $89.0\% \pm 6.2\%$, $P < 0.001$). Regardless of the ventilatory mode, mean relative humidity significantly differed between the 2 heater-humidifiers ($89.6\% \pm 6.7\%$ vs $78.7\% \pm 6.8\%$, $P = 0.003$). The in-vivo study included 10 neonates (mean $\pm$ SD gestational age: 25.7 ± 0.9 weeks and birth weight: 624.4 ± 96.1 g). Mean relative humidity during HFOV was significantly lower than during IPPV ($74.6\% \pm 5.7\%$ vs $83.0 \pm 6.7\%$, $P = 0.004$).

Conclusion: Relative humidity was significantly lower during HFOV than IPPV, both in vitro and in vivo. The type of heater-humidifier also influenced humidification. More systematic measurements of humidity of inspired gas, especially during HFOV, should be considered to optimize humidification and consequently lung protection in ELBW infants.

Introduction

In extremely low birthweight infants (ELBW), pulmonary fluid clearance and transcapillary water transport are crucial for pulmonary development.¹ The balance between inflammation, water transport, and upper

and deep airway humidification is critical and plays a role in surfactant production and continued lung development during the critical period when the preterm infant is dependent on mechanical ventilation.² A relatively small change (increase or decrease) in the temperature or humidity of the inspired gas may be sufficient to impair the preterm infant’s pulmonary function.³ Recommendations in this field come from adult studies, are uncertain,⁴ and stipulate that humidification must be maintained between 33 and 44 mg/L of absolute humidity (AH) and 75% to 100% of relative humidity (RH).⁵ Medical devices to heat and humidify the airways have been optimized for conventional intermittent positive pressure ventilation (IPPV) and can meet these humidification recommendations. High-frequency oscillatory ventilation (HFOV) uses very different settings than IPPV, often with high flow rates and always with small tidal volumes (V_T).⁶

Even though Tarnow-Mordi *et al.* first raised the problem of the fragility of preterm patients with inadequate humidification in 1989, very few studies have since addressed humidification in ELBW infants.⁷ In 2009, Chikata *et al.* and Nagaya *et al.* reported that humidification during HFOV bench testing may be more problematic than during conventional ventilation.^{8,9} More recently, Ralphe *et al.* dedicated a review to humidification during tracheal and noninvasive ventilation for ELBW and insisted on the relation between bronchopulmonary dysplasia and unsuitable humidification.⁴ We think, however, that conclusions based only on bench-test studies must also be examined in the light of clinical and laboratory data. One animal study has highlighted an interesting link between variation of humidification and lung inflammatory responses.¹⁰ All of these authors^{4,7-10} expressed regret about the lack of studies of humidification during ventilation.

Humidification of the preterm patient’s airways depends on multiple factors such as the ventilator, circuits, heater-humidifier, ventilatory mode and settings, and environmental factors.⁴ We chose to study two of these: the heater-humidifier and the ventilatory mode. Hence, our aims were, first, to bench test recent heater-humidifiers during IPPV and HFOV, and, second, to compare in-vitro and in-vivo humidification achieved in each mode. Our hypothesis was that the specific parameters of HFOV could result in less adequate humidification in this mode than during IPPV.

Materials and methods:

Our study comprised two phases: a bench-test study and a prospective observational clinical study.

Phase one (n=12): Bench-test study

The ventilator was the VN500 (Dräger Lubeck, Germany) in volume guarantee (VG) mode during both IPPV (IPPV-VG) and HFOV (HFOV-VG). The ventilatory settings were the parameters usually used in clinical settings for each mode and repeated at each set of experiments. During IPPV, we targeted a V_T of 4 mL with positive end-expiratory pressure set at 4 mbar, frequency at 50/min and an inspiratory time of 0.3 seconds. During HFOV-VG, we targeted a V_T of 2 mL, with frequency set at 12 Hz (720/min), mean airway pressure at 12 mbar, and the inspiratory/expiratory time ratio at 1:1 (i.e., an inspiratory time of 0.042 sec).

The test lung was located in a Giraffe⁷ closed incubator (GE Healthcare, USA) with heat set to 37deg C. The compliance of the test lung was calibrated around 0.3 mL/mb $\pm$ 5%, to be close to the usual lung compliance of ELBW patients.¹¹

To test the influence of heating devices on humidification, we conducted the experiments with 2 heater-humidifiers: the MR850⁷ with a RT265⁷ as the ventilator circuit, referred to hereafter as MR-A and the MR950⁷ with the 950-N81⁷ circuit (F&P, Auckland, New Zealand), referred to as MR-B. The heater-humidifiers were in automatic mode without any settings to adjust. For the RT265 circuit, we used a 30 cm extension circuit without wireless heating inside the incubator to leave the temperature sensor outside the incubator. The RT 950-N81 circuit did not necessitate an extension and was directly connected to the Y-piece.

We used the procedure described below to conduct 12 experiments (6 with MR-A and 6 with MR-B). First, the ventilatory circuit was dried until RH < 2% was reached. Then, we started ventilation and humidification in the randomly selected ventilatory mode — HFOV-VG or IPPV-VG — for at least one hour without recording. Humidity and temperature recording started after one hour and lasted for 4 hours:

2 hours in the first ventilatory mode (IPPV-VG or HFOV-VG) and 2 hours in the other mode. The first ventilatory mode was selected randomly, via sealed envelopes.

Phase two: in-vivo study

This prospective observational study took place between January 2021 and January 2022 in the neonatal intensive care unit (NICU) of the Centre Hospitalier Intercommunal de Creteil. We included ELBW born [?] 28 weeks of gestational age with a body weight of less than 1500 g at the time of the study and requiring mechanical ventilation. Patients were included in the analysis when a recording of humidity was possible in both IPPV and HFOV during their ventilatory support course. The choice of ventilatory mode and ventilatory settings were left to the clinician's expertise and were not modified due to the study. Parents were informed of the study and stated that they did not object. The institutional ethics committee approved the study on December 1, 2020. The number of subjects to include could not be predicted because the difference of inspired airway humidity between the two ventilatory modes has never been described. Thus, the study duration was set at one year.

The standard Y-piece was replaced by a sterilized Y-piece equipped with a hygrometer during nursing care to record the humidity and temperature. This recording lasted for two hours for each patient and each ventilatory mode. The Y-piece with the hygrometer was removed the next time a nurse attended the baby. Ventilator settings, heater-humidifier device information (chamber inlet and outlet temperature and flow rate), ambient temperature, and barometric pressure were all collected during the 2-hour recording. After a stabilization period, any intervention (such as opening the incubator or changing ventilatory settings) during the 2-hour recording period was recorded. Only MR-B was used as a heater humidifier to adhere to the airway humidification protocol in the NICU.

Relative humidity and temperature measures

For both in-vitro and in-vivo experiments, RH and temperature were recorded in the Y-piece just before the endotracheal tube (ETT) with a capacitive thermohygrometer and a sensor 4 mm in diameter (Testo Hygrometer 635-2[?] with sensor 2135[?], Forbach, France). The hygrometer was able to record data for a predetermined period of time (4 hours for in-vitro-study and 2 hours for in-vivo study) at a predetermined frequency (every 1 minute). The recordings were converted into two curves: RH (in %) and temperature (in degC) with PC-software (Testo Comfort Software x35 professional[?], Forbach, France). For analysis, we considered only the second hour of recording in each ventilatory mode. The first hour was considered a stabilization period. AH (in mg/L) was calculated with the following mathematical formula: $(287.7 \times RH \times Psat)/(T+273)^{12}$ with the saturated vapor pressure of water (Psat) expressed as mm Hg and temperature (T) as degC.

Beforehand, the introduction of the hygrometer into the Y-piece was tested to make sure that there was no pressure change.

Statistical analysis:

Data were described as means and their standard deviations. We compared relative and absolute humidity during IPPV versus HFOV during both the in-vitro and in-vivo experiments. We compared humidity during IPPV versus HFOV with two different heater-humidifiers (MR-A and MR-B) only during in-vitro experiments. Paired Wilcoxon tests were used in the bench tests to compare HFOV vs IPPV as the comparisons were made at the same time with the same environmental conditions. Comparisons between MR-A and MR-B used Mann-Whitney tests. In the in-vivo study, because the two modes were tested at two potentially separated periods, we used Mann-Whitney tests rather than paired tests. A *P*-value [?] 0.05 was considered significant.

Results:

Bench testing

RH (Figure 1) and AH were significantly lower during HFOV than during IPPV while temperature in the Y-piece was significantly higher during HFOV than IPPV (Table 1). RH was significantly higher with MR-A than MR-B, regardless of the ventilatory mode ($89.6\% \pm 6.7\%$ vs $78.7\% \pm 6.8\%$; $P = 0.003$) and in each ventilatory mode (Table 1, Figure 1).

In-vivo study

During the one-year study, 10 patients received both IPPV and HFOV and were recorded in both ventilatory modes. Because six patients were recorded in only one ventilatory mode, they were excluded from the analysis. Patients included had a mean $\pm$ SD gestational age at birth of 25.7 ± 0.9 weeks and a mean $\pm$ SD birth weight of 624.4 ± 96.1 g. Twenty recordings were made (10 in each ventilatory mode) at a mean $\pm$ SD postnatal age of 8.5 ± 7.7 days for HFOV and 10.9 ± 8.7 days for IPPV. Patients' characteristics and ventilatory parameters at the time of recording are summarized in Table 2.

RH during HFOV was significantly lower than during IPPV (Table 2). Postnatal age, weight at the procedure, and environmental parameters were comparable during HFOV and IPPV, but the heater-humidifier inlet and outlet temperatures, flow rates, tidal volumes, and pressures differed significantly (Table 2).

Discussion:

The two main objectives were to test the influence of the two ventilatory modes and simultaneously two different modern heater-humidifiers on humidification measured at the Y-piece. The two main results of this study were that humidity was lower during HFOV than during conventional ventilation and differed according to the heater-humidifier model. Results for the two ventilatory modes were consistent for the in-vitro study, with strictly controlled ventilatory settings and ambient conditions, and the in-vivo study, with its various ventilatory settings and ambient conditions. Several hypotheses may explain these results. The first and most intuitive explanation for this difference is that HFOV flow rates are much higher than IPPV flow rates.¹³ At the same time, both the inlet and outlet chamber temperatures were found to be higher in HFOV than IPPV. This finding suggests that the heater-humidifier increases the heat of the plate in order to increase the energy delivered by the heater-humidifier, which should be proportional to the air volume delivered by the ventilator. However, the heater-humidifier regulation tends to stop the heater plate when the inlet chamber temperature is high.¹³ In this situation, the water may be partially heated and the gas insufficiently humidified and heated. Nonetheless, the HFOV and IPPV chamber temperatures did not differ all that much clinically, although they were statistically different. This difference does not seem adequate to explain the temperature reduction of the heating plate.¹³ A second explanation might be the frequency difference. For the same duct diameter, the thermal losses of the oscillatory flow increase with its frequency.¹⁴ Thus we can expect that this increasing loss will decrease temperature and AH. However, Nagaya *et al.* showed that the temperature change in the ETT did not depend on the oscillatory frequency when the oscillatory volume was fixed; but, the temperature did depend on the oscillatory volume when the oscillatory frequency was fixed.¹⁵ It is also interesting to note the previous observation during IPPV that AH decreases linearly with the value of V_T ,¹⁶ although the reasons for this phenomenon remain unclear.

Recommendations to target a RH of inspired gas between 75% and 100% come from recommendations for adults, but ventilation in ELBW patients is very different from that in adults, due to the use of low tidal volumes and high instrumental dead space. Because of these particularities, humidity at the tip of the ETT is different from that at the Y-piece.¹⁵ Thus, it might not be possible to extrapolate adult recommendations on humidification to preterm neonates, who might even need higher levels of humidity.

It is important to note that the mean RH during HFOV in our study was below the recommended 75%. Poor humidification may have a deleterious effect on inflammation^{10 17} and on water movements¹⁸ at the respiratory tract level as well as at the cellular level. It may thus impair lung development as it can induce such adverse events as atelectasis or plugged ETT and unplanned extubations. The incidence of inadequate humidity as an associated risk factor of pulmonary inflammation and consequently part of ventilator-induced lung injury is poorly documented. The principal reason for the lack of literature on this subject may well be the lack of routine monitoring of humidity and temperature of inspired gases. This study presents a method

for exploring humidity and temperature at the Y-piece during tracheal ventilation that could be routinely used for in-vitro and in-vivo studies. Monitoring humidity at the Y-piece is a first approach and is not yet sufficient to extrapolate the real humidity level in the trachea.

The superiority of HFOV over IPPV for lung protection has not yet been proven,¹⁹ although we might expect superiority due to the use of lower tidal volumes⁶ in this ventilatory mode in preterm patients.²⁰ IPPV with volume guarantee mode induces lower expression of early inflammation markers than HFOV,²¹ which is contradictory to the expected protective effect of HFOV. Our study suggest that inadequate humidification could be a factor explaining potential excess inflammation during HFOV. Another important result of this study is that humidification is not easily predictable and depends not only on ventilation mode but also on the type of circuit and the specific heater-humidifier used.

Our study has several limitations. First, it is an observational study. An interventional study, however, appears difficult to conduct, given the variety of factors involved in determining the humidity level: the medical devices used, the ventilatory settings, and ambient conditions. In this in-vitro and in-vivo study, the only ventilator used was the Drager VN500. One advantage of using a single ventilator is the homogeneity of the study conditions, but its negative aspect is that we cannot extrapolate these results to other ventilators. The specific flow management of the VN500 during HFOV may influence the hygrometric results as the flow is quadrupled during HFOV compared to conventional IPPV. Nevertheless, because other ventilators do not systematically provide flow rates, it seems difficult not to remain vague for the moment. While waiting for humidity monitoring which is technically more difficult, we think that flow rate monitoring should be systematically reported for ventilators.

In conclusion, we found that during mechanical ventilation, humidity measured in-vitro and in-vivo in ELBW preterm infants was lower with HFOV than with IPPV and did not reach recommended values during HFOV. Moreover, humidification values differed significantly according to the humidifier device used. These results suggest that humidification depends on ventilatory mode and heating devices and that HFOV requires a specific humidification management. It is suggested that the systematic control of humidity, temperature, and flow rate during mechanical ventilation may optimize lung protection strategies.

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