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The effect of decoupling humidity control on aerosol drug delivery during HFNC for infants

(MSc) Madeline X. Zhang[1, *], (MD PhD) Reinout A. Bem[2], (MSc) Tom Huijgen[3], (Msc) Rozalinde Klein-Blommert[2], (PhD) Daniel Bonn[1] and (PhD) Cees J.M. van Rijn[1]

[1]Institute of Physics, Van der Waals-Zeeman Institute, University of Amsterdam, Amsterdam, the Netherlands

[2]Department of Pediatric Intensive Care, Emma Children's Hospital, Amsterdam University Medical Centers, location University of Amsterdam, Amsterdam, the Netherlands

[3]Medspray BV, Enschede, the Netherlands

Location: The study was performed at the University of Amsterdam, Amsterdam, the Netherlands and Medspray BV, Enschede, the Netherlands.

Affiliations: Madeline X. Zhang is affiliated with the Institute of Physics, Van der Waals-Zeeman Institute, University of Amsterdam, Amsterdam, the Netherlands. Reinout A. Bem is affiliated with the Department of Pediatric Intensive Care, Emma Children's Hospital, Amsterdam University Medical Centers, location University of Amsterdam, Amsterdam, the Netherlands. Tom Huijgen is affiliated with Medspray BV, Enschede, the Netherlands. Rozalinde Klein-Blommert is affiliated with the Department of Pediatric Intensive Care, Emma Children's Hospital, Amsterdam University Medical Centers, location University of Amsterdam, Amsterdam, the Netherlands. Daniel Bonn is affiliated with the Institute of Physics, Van der Waals-Zeeman Institute, University of Amsterdam, Amsterdam, the

Netherlands. Cees J.M. van Rijn is affiliated with the Institute of Physics, Van der Waals-Zeeman Institute, University of Amsterdam, Amsterdam, the Netherlands.

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Correspondence: Madeline X. Zhang. Institute of Physics, Van der Waals-Zeeman Institute, University of Amsterdam, Amsterdam, the Netherlands. E-mail: x.zhang4@uva.nl.

Abstract

BACKGROUND: Aerosol therapy is commonly used during treatment with high-flow nasal cannula (HFNC) in the intensive care unit (ICU). Heated humidification inside the HFNC tubing circuit leads to unwanted condensation, which may greatly limit the efficiency of drug delivery. In this study, we aimed to investigate whether a novel humidification system, which decouples temperature and humidity control, can improve the delivered dose.

METHODS: In a bench study setup, fluorescein sodium solution was nebulized using a vibrating-mesh nebulizer in an infant HFNC circuit to measure the delivered dose, with a conventional versus a novel decoupled humidifier. The deposition of fluorescein inside each breathing circuit component and a final collection filter at the end of the nasal cannula was collected and quantified with a UV-vis spectrometer. Droplet sizes at different sections of the breathing circuit were measured by laser diffraction. Three air flow rates: 5, 10 and 15 L/min, and two nebulizer positions: (1) at the humidifier and (2) after the inspiratory tube, were tested.

RESULTS: The delivered dose decreased with increasing flow rate for the conventional setup and was higher when the nebulizer was placed after the inspiratory tube. Turning off the conventional humidifier 10 minutes before and during nebulization did not improve the delivered dose. The decoupled humidifier achieved a significantly higher ($p = .002$) delivered dose than the conventional setup. The highest delivered dose obtained by the decoupled humidifier was 62.4% when the nebulizer was placed after the humidifier, while the highest dose obtained for the conventional humidifier was 36.3% by placing the nebulizer after the inspiratory tube.

CONCLUSIONS: In this bench study, we found that the delivered dose for an infant HFNC nebulization setup could be improved significantly by decoupling temperature and humidity control inside the HFNC circuit, as it reduced drug deposition inside the breathing circuit.

Key words: HFNC; respiratory support; nebulization; humidification; aerosol therapy; drug delivery

Introduction

Aerosol therapy (e.g. nebulization of mucolytics and bronchodilators) is a common treatment for critically ill patients, including children, admitted to the intensive care unit (ICU) [1][2][3][4]. In the ICU, aerosol therapy is often performed during various respiratory support modalities. One such respiratory support commonly used for pediatric patients is high-flow nasal cannula (HFNC), where a warm and humidified mixture of air and oxygen is delivered to the patient at relatively high flow rates through a nasal cannula with nasal prongs. Recently, there has been an increase in the routine use of aerosol therapy during HFNC [5]. However, there are concerns about the efficacy of nebulization during HFNC [6] as many studies reported that less than 20% of the nebulized dose reaches the patient's lungs [5][7].

Many parameters have been shown to affect the delivered dose during HFNC, such as ventilator flow rate, nebulizer type and nebulizer position [7][8]. It was found that a low flow rate is more beneficial [7], mesh nebulizers are more efficient than jet nebulizers [6] and placing the mesh nebulizer before the humidifier gives a higher delivered dose [8]. Similar observations have been made for pediatric HFNC in terms of flow rate [9][10][11], nebulizer type [12] and nebulizer position [9], although the effects of the various parameters for HFNC for pediatric setups are less well studied than adult setups [13]. One other factor that poses a main limitation to effective/efficient nebulization during HFNC appears to be humidification, as high relative humidity may lead to undesired condensation on the tubing walls [14], and hence increased drug deposition in the tubing. It was observed that a higher dose could be delivered under non-humidified (dry) conditions for adult HFNC, especially at high flow rates [15]. Furthermore, it was found that using a heated and humidified HFNC setup may result in a clinically significant amount of condensation water reaching the upper airway of preterm infants [16]. Although high relative humidity is shown to negatively affect drug nebulization efficacy, it is currently not possible to control humidity independently from temperature as the conventional humidification devices in the ICUs

humidify the air using water vapor where the relative humidity is always near 100% [17][18].

This study aims to improve the delivered dose of infant HFNC nebulization setups by controlling the humidity independently. To do so, we use a novel humidification device able to decouple the temperature and humidity control inside the breathing circuit for the first time. The novel system is expected to improve drug delivery efficacy in two ways: firstly, by minimizing the formation of condensation during humidification, and secondly, by turning off humidification but not gas heating during nebulization, it allows partial drug aerosol evaporation to take place, thereby minimizing deposition in the breathing circuit. The performance of an infant HFNC setup incorporating the novel humidification device is evaluated in terms of delivered dose and compared with the conventional setup.

Methods

HFNC circuit setup

The study was performed using an experimental bench setup replicating the infant HFNC setup in the pediatric ICU at the Amsterdam University Medical Center (AUMC) hospital. In the lab, dry air from an air compressor was used as the air supply to the HFNC circuit. The HFNC circuit consists of several components: the humidification system, the inspiratory tube, the nasal cannula, the T-piece and the nebulizer.

Two different humidification systems as shown in Figure 1 were tested and compared. The first is the conventional coupled heater/humidifier device currently used for HFNC in the ICU, shown in Figure 1a. This humidifier (F&P 950, Fisher & Paykel, Auckland, New Zealand) consists of a pot containing water heated by a heating plate underneath. This humidifier also controls the active heating of its specialized pediatric inspiratory tube (Neonatal Optiflow Junior heated circuit kit 950N40, 11mm inner diameter, Fisher & Paykel, Auckland, New Zealand). For this humidifier, the target temperature at the patient was set at 37°C, and the humidity level cannot be controlled independently. To study the effect of turning off this humidifier on the delivered dose for this setup,

we first ran the system at the chosen flow rate (15 L/min) with the humidifier turned on until its display indicated it had reached the target 37°C. Subsequently, the humidifier (along with the tubing heating) was turned off and we waited 10 minutes before starting nebulization. The humidifier was kept off during nebulization for this test. For all other experiments with this humidifier, the humidifier was kept on before and during nebulization.

The second type of humidifier tested is a novel system, shown in Figure 1b, where the temperature and humidity can be controlled separately through a heater and a spray chamber. A different inspiratory tube (Ventstar pediatric tubing, 11mm inner diameter, Draeger, Lübeck, Germany) than the one used for the conventional humidifier was used; it was not possible to use the same tubing for the two humidifiers because the conventional humidifier tubing is only compatible with the conventional humidifier. The humidifier and the inspiratory tube can be viewed as a package which together controls the temperature and humidity inside the breathing circuit. Therefore, an inspiratory tube with a similar heating mechanism (embedded heated wire and smooth bore) and tubing inner diameter was used for the decoupled humidifier. The decoupled humidifier was also set up to achieve 37°C at the patient, both with and without active humidification. The target absolute humidity during HFNC when there is no nebulization is 40 mg/L. The following procedure was performed during experimental measurements with the decoupled humidifier: before nebulization, the system was turned on, where a pump added moisture inside the circuit by spraying a fine mist of water. To provide the required energy to turn the mist into water vapor, the air was heated up just upstream of the spray injection point. Once the temperature and humidity measured at the end of the nasal cannula stabilized (no significant fluctuations) after around 10 minutes, the liquid pump was turned off and the heater was turned to a lower setting to maintain the gas temperature. The temperature and humidity probe was removed and the collection filter was attached. Nebulization started 5 minutes after the liquid pump was turned off.

After leaving the humidifier, the warm humidified air is further actively heated in the inspiratory tube until it reaches the nasal cannula which no longer has active heating. For this study, experiments were conducted at three different infant HFNC air flow rates (5, 10 and 15 L/min). A single infant nasal cannula (OPT316 Optiflow Junior Infant Nasal Cannula, Fisher & Paykel, Auckland, New Zealand) suitable for this range of flow rates tested

was used for all experiments.

A vibrating mesh nebulizer (Aerogen Solo, Aerogen, Galway, Ireland) was chosen because it can achieve higher drug deposition in the patient than a jet nebulizer [8], attributed to a higher respirable fraction of aerosols and lower residual dose [19][20]. Figure 2 shows the nebulization breathing circuit used in the experiments, including the two feasible nebulizer positions to be tested for each humidifier. For the conventional humidifier setup (Figure 2a), the nebulizer positions are before the humidifier and after the inspiratory tube. For the decoupled humidifier setup (Figure 2b), the two nebulizer positions are after the humidifier and after the inspiratory tube.

Temperature and humidity measurements

To observe the gas conditions inside the HFNC circuit, the temperature and humidity at the end of the inspiratory tube were measured with a temperature and humidity sensor (SHT4x, Sensirion AG, Stäfa, Switzerland) while the temperature and humidity at the end of the nasal cannula were measured with a different temperature and humidity sensor (EE33, E+E, Engerwitzdorf, Austria). Each measurement was repeated three times. These measurements were performed separately from the delivered dose measurements so that the sensors would not influence the depositions.

Quantification of delivered dose

The primary outcome of this study was the dose captured in an absolute filter (Respirgard II 303, CareFusion, San Diego, CA, USA) at the end of the nasal cannula, representing the delivered dose through the nasal prongs which is also the exposure dose to the patient. A secondary outcome is the deposited dose in each component of the HFNC circuit. A fluorescein sodium solution was used to model aerosol drug formulations in order to quantify the delivered dose and visualize depositions inside the various HFNC setup compartments. The solution is made from dissolving fluorescein sodium powder (C.I.45350 (Acid Yellow 73), Aldrich, Burlington, MA, USA) in demineralized water and filtered before usage to prevent nebulizer clogging due to impurities in the

solution. 3 mL of 0.2% (w/w) fluorescein sodium solution was placed in the nebulizer drug compartment and nebulized to completion. The fluorescein sodium aerosols then deposited in various locations in the tubing, connectors as well as in the collection filter.

At the end of the experiment, all components of the circuit were disconnected, and each component was thoroughly rinsed with demineralized water and the obtained solution was collected as the sample. The solution was then further diluted and quantified by measuring the absorbance at 460 nm using a UV-Vis spectrometer (Evolution 201, Thermo Fisher Scientific, Waltham, MA, USA). Knowing the dilution procedure of the breathing circuit samples, the dose in each component was calculated as the ratio between the mass of fluorescein sodium in that component to the mass of the total amount of fluorescein sodium nebulized in the circuit.

Droplet size measurements

To investigate differences in deposition for the various setups, the droplet size distributions at the different sections of the circuit were obtained using a laser diffractor (Spraytec, Malvern Panalytical, Worcestershire, UK) as an additional secondary outcome. During droplet size measurements, isotonic saline solution (0.9% sodium chloride injection solution) was used for nebulization. The isotonic saline solution was used instead of water for injection to prevent the self-charging phenomenon during nebulization with the mesh nebulizer. Since water for injection is a non-conductive liquid, it leads to electrostatic charging of the droplets during nebulization which causes the droplets to fly towards the inner walls of the T-piece and reduces the nebulizer output to nearly zero. Using isotonic saline prevents this phenomenon and enables meaningful droplet size measurements. It is also more comparable to the (often electrically conductive) inhalation drug solutions used in the ICU. The measurements were performed less than 2 cm from the end of the breathing circuit to minimize evaporation in the free air. The result was averaged over a fixed time interval with outliers removed. The median droplet size (Dv50) of each distribution was computed by the Spraytec software.

Statistical analysis

Statistical analysis was performed for the primary outcome. Each delivered dose quantification test case was repeated three times. The mean and standard deviation of each independent test case performed in triplicates were calculated. A two-sample Welch T-test was used to check for statistical significance when comparing two independent values (statistical significance defined as $p<.05$). Differences in means between the delivered dose for the three flow rates, two nebulizer positions and two types of humidifiers were evaluated using two-way factorial analysis of variance (ANOVA). Statistical analyses were performed in R.

Results

Effect of flow rate, nebulizer position and humidification on the conventional humidifier setup

Figure 3 shows the effect of air flow rate and nebulizer position on the deposition in various components of the HFNC circuit. The delivered doses for various flow rates and nebulizer positions for the conventional humidifier setup are summarized in Supplementary Table S1. When the nebulizer was placed before the humidifier, as is common practice in the ICU, the delivered dose decreased with increasing flow rate. Drug losses occurred mainly in the nasal cannula and the inspiratory tube. In the inspiratory tube, the tubing section near the integrated sensor turned visibly yellow from accumulated fluorescein sodium during the experiments (Supplementary Figure S1), while condensation water was observed to accumulate inside the small, bifurcated tubing of the nasal cannula (Supplementary Figure S2). Deposition in the inspiratory tube increased with the flow rate. It shows that the delivered dose of the conventional humidifier setup was generally low, with a highest delivered dose (collection filter dose) of 25.3% ± 5.5% at 5 L/min and a lowest delivered dose of 12.0% ± 0.7% at 15 L/min. The deposition in the collection filter was higher when the nebulizer was placed after the inspiratory tube, and the dependence on the flow rate became less. The increase in delivered dose due to the change in nebulizer position was significant at 10 L/min ($p=.049$) and 15 L/min ($p=.039$), but not at 5 L/min ($p=.76$). A maximum delivered dose of 36.3% ± 8.6%

was achieved at 10 L/min. As the nebulizer was placed after the inspiratory tube, there was no deposition in the inspiratory tube. However, there was more deposition in the nasal cannula and the T-piece than when the nebulizer was placed before the humidifier. A two-way factorial analysis of variance (ANOVA) suggests that the nebulizer position had a significant effect on the delivered dose ($p=.001$) for all flow rates, while the flow rate did not have a significant effect for both nebulizer positions ($p=.26$). The interactive effect of nebulizer position and flow rate on the delivered dose was not significant ($p=.053$)

To investigate the effect of humidification for the conventional humidifier setup, we obtained the delivered dose of the humidifier when it was turned off for 10 minutes to compare that with the delivered dose when the humidifier was left on. The nebulizer was placed before the humidifier and a flow rate of 15 L/min was used for this comparison since this flow rate gave the lowest delivered dose (according to Figure 3) for this nebulizer position. Contrary to what is expected, turning the humidifier off resulted in a significantly ($p=.011$) lower delivered dose (7.5% ± 1.3%) than when the humidifier was on (12.0 % ± 0.7%). Supplementary Figure S3 shows the temperature, absolute humidity and relative humidity at the end of the inspiratory tube during the 10 minutes after turning off the humidifier. The relative humidity increased by 1.8% (from 78.9% to 80.7%), while the absolute humidity in the system was reduced by 52% (from 38.9 to 18.6 g/m^3) in 10 minutes. In fact, the relative humidity in the tubing first increased to up to 91.6% before dropping again.

The droplet size distribution of aerosols exiting the T-piece, the inspiratory tube and the nasal cannula were obtained by the laser diffraction setup. The median droplet sizes (Dv50) for different cases with the conventional humidifier are shown in Supplementary Table S2. The droplet size immediately after the T-piece was similar for all flow rates. The droplet size was smaller at the end of the inspiratory tube than before the inspiratory tube, and this reduction in droplet size was slightly more pronounced for higher flow rates. The droplet sizes were further reduced at the end of the nasal cannula.

When the nebulizer was placed after the inspiratory tube, at 5 L/min, the droplet size after the nasal cannula was similar to when the nebulizer was placed before the humidifier. The droplet size after the nasal

cannula decreased more with increasing flow rates when compared to placing the nebulizer before the humidifier. At 15 L/min, the droplets could no longer be measured by the laser diffractor, possibly due to the low droplet concentration.

When the humidifier was turned off for 10 minutes before nebulization, the droplet size at the end of the inspiratory tube did not change by more than 0.1 µm when compared to the case with the humidifier on. The droplet size at the end of the nasal cannula became slightly (0.2 µm) larger.

Effect of independent humidity control with the decoupled humidifier

Figure 4 shows the deposition in various components of the breathing circuit for different flow rates and nebulizer positions for the novel decoupled humidifier setup. For this humidifier, placing the nebulizer after the humidifier led to a higher delivered dose than placing it after the inspiratory tube. Placing the nebulizer after the inspiratory tube led to significant deposition in the nasal cannula, more than twice the deposition in the collection filter at high flow rates. Placing the nebulizer after the humidifier led to 45.2% - 62.4% delivered dose for the range of flow rates tested. The highest delivered dose of 62.4% ± 6.4% was obtained at 10 L/min. For this nebulizer position, the highest losses in the circuit occurred in the nasal cannula and the T-piece, while the deposition inside the inspiratory tube was relatively low (<10%).

Figure 5 shows the comparison between the conventional setup and the decoupled humidifier setup in terms of deposition in all circuit components when the nebulizer was placed near the humidifier. For the conventional setup, the nebulizer was placed before the humidifier as in the ICU, while for the decoupled setup, the nebulizer was placed after the humidifier. The delivered doses for the conventional and decoupled humidifier setup at various flow rates are summarized in Supplementary Table S3. At a flow rate of 15 L/min, the decoupled humidifier setup (57.5% ± 3.5%) achieved a delivered dose around five times the dose of the conventional humidifier setup (12.0% ± 0.7%) currently used in the ICU. The decoupled humidifier setup is considered to have had a significantly higher ($p=.002$) delivered dose than the conventional setup. A two-way factorial analysis of variance (ANOVA) suggests that the humidifier type had a significant effect on the delivered dose ($p<.001$) while the flow

rate did not (p=.87). The interaction effect of humidifier type and flow rate on the delivered dose was also significant (p=.002).

During HFNC with active humidification and no nebulization, the absolute humidity at the end of the inspiratory tube was 38.1±1.8 mg/L for a flow rate of 15 L/min, 41.0±1.4 mg/L for a flow rate of 10 L/min and 34.3± 5.1 mg/L for a flow rate of 5 L/min. Table 1 summarizes the relative humidity inside the inspiratory tube at the beginning (immediately before the nebulizer was turned on and 5 minutes after the active humidification was turned off) and at the end of nebulization for different flow rates for the decoupled humidifier setup. The decoupled humidifier setup was not actively humidifying the air immediately before nebulization and had a much lower relative humidity than the coupled humidifier which had near 100% relative humidity. No condensation was observed before nebulization for the decoupled humidifier. Table 1 also shows that the aerosols generated by the nebulizer increased the humidity inside the tubing.

Supplementary Table S4 shows the median droplet size (Dv50) after the T-piece and after the inspiratory tube for various flow rates when the nebulizer was placed after the humidifier for the decoupled humidifier setup. It can be observed that the droplet size reduced more in the inspiratory tube for higher flow rates. At 15 L/min, the droplets exiting the inspiratory tube could not be measured anymore, probably due to small diameters and low droplet density. Furthermore, there is more reduction of droplet size in the inspiratory tube at 10 L/min and 15 L/min for the decoupled humidifier setup when compared to the conventional coupled humidifier setup.

Discussion

The main goal of this study was to investigate whether decoupling humidity control from temperature control could improve the delivered dose (primary outcome) during aerosol therapy for an infant HFNC setup. Using a novel decoupled humidifier, we found that independent control of humidity and gas temperature during nebulization led to a significantly higher delivered dose than the conventional coupled humidifier setup for all flow

rates tested, as partial evaporation of the nebulized aerosols led to less deposition inside the breathing circuit while maintaining sufficient relative humidity.

In the context of aerosol therapy during HFNC, this is the first study to address the negative effect of high relative humidity levels in the breathing circuit on the delivered dose. We showed that the delivered dose could not be improved by turning off the conventional humidifier shortly before nebulization as it did not lead to a sufficient decrease in relative humidity. To address the limitations of the conventional humidifier, we replaced it with a novel decoupled humidifier and demonstrated the new setup's ability to improve the delivered dose by reducing deposition in the breathing circuit. Although tested on an infant HFNC setup, the decoupled humidifier is likely to improve the delivered dose for other patient groups as well, which could be a subject of further study. The increase in the delivered dose potentially enables aerosol therapy to become more efficient and effective during HFNC treatment of patients in the ICU.

Conventional humidifier setup

For validation, we first studied the conventional HFNC setup at various flow rates and nebulizer positions. Our results showed that a higher air flow rate led to a lower delivered dose when the nebulizer was placed before the heated humidifier. This negative influence of higher flow rates is consistent with findings in the literature [7][9][10][11]. To understand why this is the case, we measured the droplet size distribution in the breathing circuit and deduced that undesired deposition in the circuit is likely due to two different contributions, both of which could result in the observed reduction of droplet size: 1) the collision of (larger) droplets into tubing structure due to inertial impact and turbulence, and 2) absorption of droplets into the condensation of water vapor on the inner walls of the circuit. At high flow rates, the larger droplets are more likely to hit the wall or the integrated sensors in the tubing as they are less able to follow or drift in the airflow. There is also more turbulence in the tubing at higher flow rates, leading to more local deposition. Condensation mainly occurred inside the nasal cannula, likely due to the temperature drop from the heated inspiratory tubing to the unheated nasal cannula.

In addition, our results showed that the delivered dose of the conventional setup at higher flow rates could

be improved by placing the nebulizer after the inspiratory tube. This is contradictory to previous adult [8] and pediatric results [9] in the literature, for which it was found that placing the nebulizer before the humidifier led to a higher delivered dose. This can be likely attributed to the different humidifiers and inspiratory tubes used. Our study is the first on the topic using the F&P 950 humidifier system. The relevant adult [8] and pediatric [9] studies in the literature used different humidifier systems such as the F&P 850 which have different inspiratory tubes with very different internal structures and tube heating that would lead to very different depositions. Hence, it is not possible to make a fair comparison between our results and the literature due to the difference in the equipment used without looking into the effect of these structural and functional differences on deposition.

Furthermore, our study showed that turning off the humidifier briefly before and during nebulization did not improve the delivered dose, because of the high relative humidity that remains in the circuit tubing. The relative humidity in fact increased due to the drop in temperature and the presence of condensation in the breathing circuit, despite a significant drop in the absolute humidity. This implies that evaporation in the tubing was not enhanced as hoped, as corroborated by the droplet size measurements. Overall, this shows that turning off the humidifier briefly before nebulization is not a feasible solution for improving the delivered dose of the HFNC nebulization system. This result adds weight to the recommendation against turning off the humidifier during HFNC in addition to safety concerns [8][21]. More importantly, this demonstrated the need for a decoupled humidification system, as it's currently not possible to lower the air humidity independently from temperature.

Decoupled humidifier setup

As the conventional humidifier was not able to address the relevant concerns, we replaced it with a novel decoupled humidifier which enables independent control of heating and humidification in the HFNC circuit. During nebulization, the conventional humidifier humidifies the air by heating a pot of water while the decoupled humidifier humidifies the air by (partially) evaporating the nebulized drug aerosols. For the decoupled humidifier, placing the nebulizer after the humidifier was more advantageous than placing it after the inspiratory tube. This is

mainly due to differences in deposition in the nasal cannula. When placing the nebulizer at the humidifier, as the droplets travel through the inspiratory tube where the relative humidity is low, they experience partial evaporation before flowing into the nasal cannula. These droplets entering the nasal cannula are then smaller and thus less likely to hit the tubing wall.

When the nebulizer was placed near the humidifier, the novel decoupled humidifier setup gave a much higher (around five times) delivered dose than the conventional humidifier setup, especially at high air flow rates. One obvious contribution to the improvement is that the aerosol no longer passed through the heated water pot, where around 10% of the drug was lost. The more significant contribution was due to decreased undesired deposition in the inspiratory tube and nasal cannula. By turning off any active humidification during nebulization, the warm and low-humidity environment inside the tubing caused the nebulized aerosols to evaporate partially, which increased the relative humidity inside the circuit. The smaller particles are also less likely to collide with the internal structures, thereby reducing deposition in the inspiratory tube and nasal cannula. As a result, the delivered dose for the decoupled humidifier setup was no longer limited at higher flow rates.

Clinical outlook

This study functions as a proof-of-principle and focuses on an infant HFNC setup. This is because the problem with condensation due to heated humidification is most pronounced for infant HFNC circuits due to the small tubing diameters, and the consequences of this condensation liquid potentially entering the airway are more severe for infants than larger patients [16]. In its current state of development, the decoupled humidifier cannot yet be safely used on patients, awaiting further optimization and research for formal medical device applications. Theoretically, this type of novel humidifier could be used by clinicians in all situations where active humidifiers are currently used, e.g. HFNC, invasive mechanical ventilation, CPAP and under certain (pre-)anesthesia settings, for patients of all ages. However, more extensive testing on a wider range of flow rates is required for application in other patient groups. The advantage of the decoupled humidifier is that clinicians will have the freedom to individually set the desired level of absolute humidity and temperature for their patients through the decoupled

heater and humidifier. To optimize intermittent aerosol therapy during HFNC, a function could be built where the clinician can temporarily reduce the absolute humidity delivered by the system for a limited duration (e.g. 10 minutes), after which the system will automatically revert to the original absolute humidity setting. In this time window, the clinician can apply aerosol therapy with significantly higher efficiency. Although active humidification was turned off completely during nebulization in this study, it is possible to set a minimum humidity level (e.g. 10-20 mg/L) to increase the relative humidity at the end of the nasal cannula based on patient requirements and air flow rates. In case the nebulizer stops unexpectedly (due to clogging, running out of medicine, etc.), the decoupled humidifier should detect and compensate for the drop in relative humidity by immediately increasing active humidification to maintain the minimum humidity level set by the user, limiting the risk of dry air entering the airway with the decoupled setup. This function needs to be demonstrated in future testing. A possible follow-up study would be to investigate the interactive effect between active humidification and the evaporation of the medical droplets, and to find an optimal balance of the two processes to achieve the optimal combination of humidification and medication delivery at a certain air flow rate.

Limitations

This study has several key limitations. Firstly, this proof-of-principle study currently only evaluated the delivered dose, meaning the dose delivered through the nasal prongs, and did not quantify the inhaled dose/lung dose which would be lower than the delivered dose due to losses in the nasal cavity and exhalation. Although breathing parameters are not expected to affect flow conditions inside the HFNC circuit and the delivered dose through the nasal cannula, they would affect the lung dose. No breathing simulator or mannequins were used in this study which may help quantify lung dose and losses in the nasal cavity. Further testing in spontaneous breathing simulations and/or research subject settings is warranted.

Secondly, the nasal cannula was positioned horizontally to prevent deposition fluids from flowing between the various compartments due to gravity. This is not the clinical practice as the nasal cannula is positioned upwards in the ICU, which leads to condensation liquid flowing to the lowest point in the circuit.

This choice of placement might have led to large variability in the delivered dose when the nebulizer was placed after the inspiratory tube for the conventional setup. This is because there was a significant amount of condensation fluid inside the tubing for this test case and some of this fluid containing drug particles could have moved downstream to the next component during the experiment, going from the T-piece to the nasal cannula and from the nasal cannula to the collection filter. This could have led to an overestimation of the collection filter dose. However, placing the nasal cannula upwards would not have avoided this issue completely, as we observed some fluid droplets shooting out of the nasal cannula when the nasal cannula was positioned both horizontally and vertically at high flow rates because of the small inner diameter of the nasal cannula tubes. The placement of the nasal cannula is not expected to affect the results significantly for the test cases with the other nebulizer position or the decoupled humidifier, as they had much less condensation. Moreover, gravity does not affect the deposition of the small droplets that would reach the patient as they are dominated by diffusion.

Furthermore, the nebulizer position near the humidifier was different for the two humidifiers. For the conventional humidifier, the nebulizer was placed before the humidifier, while for the decoupled humidifier, the nebulizer was placed after the humidifier. This was because placing the nebulizer immediately after the humidifier is not possible for this conventional humidifier due to direct electrical connections between the humidifier and the inspiratory tube required for heating control at this location. Even if it were possible, placing the nebulizer immediately after the conventional humidifier would likely lead to significant condensation and deposition in the nebulizer-humidifier connector, as corroborated by the literature with a similar humidifier setup [22], making it likely less efficient than placing the nebulizer before the conventional humidifier which is also the common clinical practice. On the other hand, it was also not possible to place the nebulizer before the decoupled humidifier as the drug aerosols would likely lose their stability and medical properties due to the heater and contaminate the heater stage. Therefore, although it would be beneficial to have direct comparisons of the two humidifiers for the same nebulizer positions, this was unfortunately not possible due to equipment constraints. However, this inconsistency in nebulizer positions between the two humidifier setups does not affect the main result, which is

that the novel decoupled humidifier setup achieved a much higher delivered dose than what is possible by the conventional setup for the flow rates tested.

Lastly, it is known that the parameters such as density, viscosity and surface tension of the nebulized solution can affect droplet size distributions and depositions. The fluorescein solution we used to visualize and quantify depositions is similar to low-concentration drugs in the ICU such as albuterol in terms of density and viscosity and it is also a salt solution. It is less representative of more viscous drugs such as antibiotics. Future testing with various drugs is needed to see how the deposition and droplet sizes might differ.

Conclusions

This work evaluated the delivered dose in aerosol therapy during HFNC treatment in a simulated infant setting for various flow rates and nebulizer positions when using a conventional humidifier versus a novel decoupled humidification system. We demonstrated that decoupling temperature and humidity control could increase the delivered dose by enabling partial evaporation of the drug aerosol. Future research and development are needed to test, validate, and incorporate the novel decoupled humidifier in a clinical setting to provide more effective aerosol therapy during HFNC for ICU patients.

Quick look:

Current Knowledge

Aerosol therapy is commonly used during HFNC in ICU but concerns about drug delivery remain. Many parameters affect the delivered dose, such as the flow rate and the nebulizer position. High relative humidity has a negative effect on the delivered dose, especially for pediatric HFNC, but it is currently not possible to control humidity independently with conventional devices where temperature and humidity control are coupled.

What This Paper Contributes To Our Knowledge

This proof-of-principle bench study demonstrated that the delivered dose during infant HFNC nebulization can be increased significantly by decoupling humidity control from temperature with a novel humidification device. The device turns off active humidification during nebulization, allowing the drug aerosols to partially evaporate and humidify the gas inside the breathing circuit, reducing undesired deposition while maintaining sufficient relative humidity inside the breathing circuit.

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Figure legends

Figure 1: Illustrations of the two different humidification systems: a) conventional coupled humidifier and b) novel decoupled humidifier.

Figure 2: Experimental HFNC setup showing the various compartments and device positions for the two humidifiers (a) conventional humidifier and (b) decoupled humidifier. Each humidifier corresponds to two different setups with different nebulizer positions as indicated.

Figure 3: Deposition (mean and standard deviation) in various breathing circuit components for two different nebulizer positions when using the conventional humidifier. CF: collection filter (delivered dose), NC: nasal cannula, TP: T-piece, N: nebulizer, IT: inspiratory tube, H: humidifier. P values are indicated for the delivered dose.

Figure 4: Deposition (mean and standard deviation) in various breathing circuit components for two different nebulizer positions when using the decoupled humidifier. CF: collection filter (delivered dose), NC: nasal cannula, TP: T-piece, N: nebulizer, IT: inspiratory tube.

Figure 5: Deposition (mean and standard deviation) in various breathing circuit components for the decoupled humidifier setup vs the conventional humidifier setup. The nebulizer was placed close to the humidifier for both setups: before the humidifier for the conventional setup and after the humidifier for the decoupled setup. CF: collection filter (delivered dose), NC: nasal cannula, TP: T-piece, N: nebulizer, IT: inspiratory tube, H: humidifier. P values are indicated for the delivered dose.

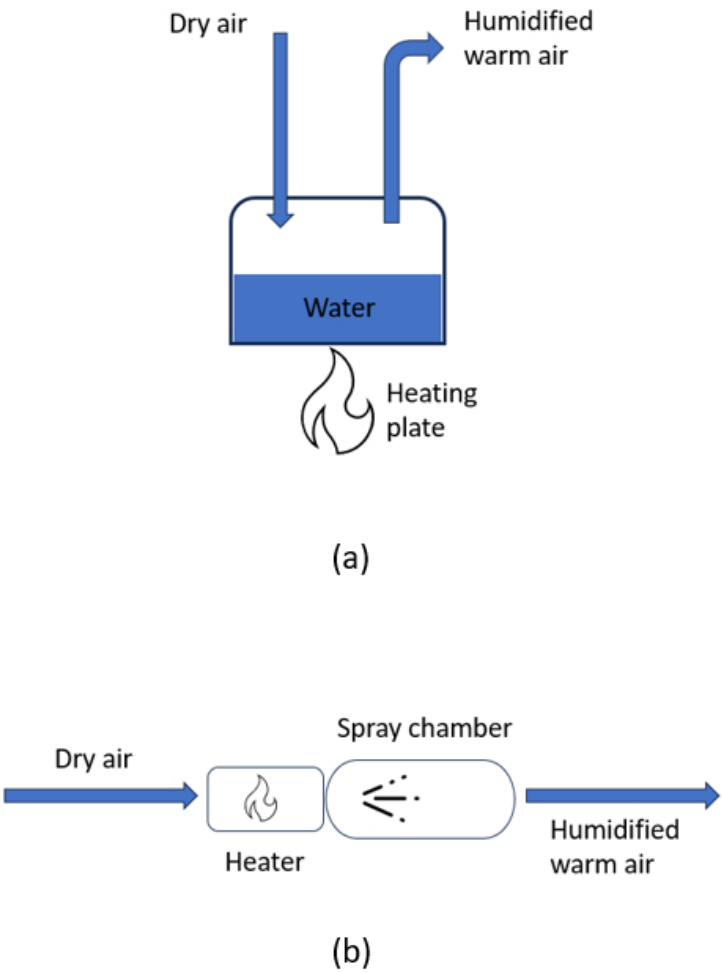

Figure 1: Illustrations of the two different humidification systems: a) conventional coupled humidifier and b) novel decoupled humidifier.

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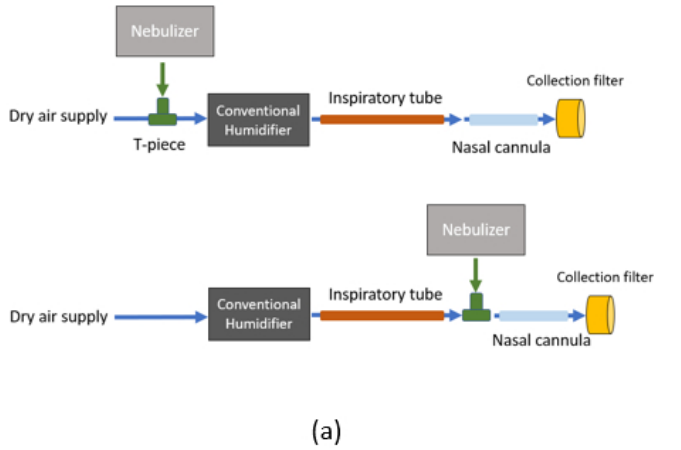

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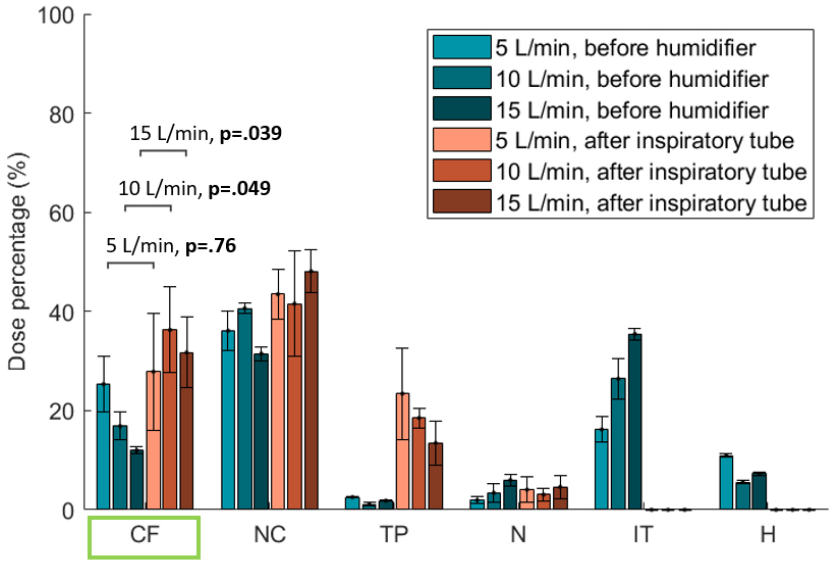

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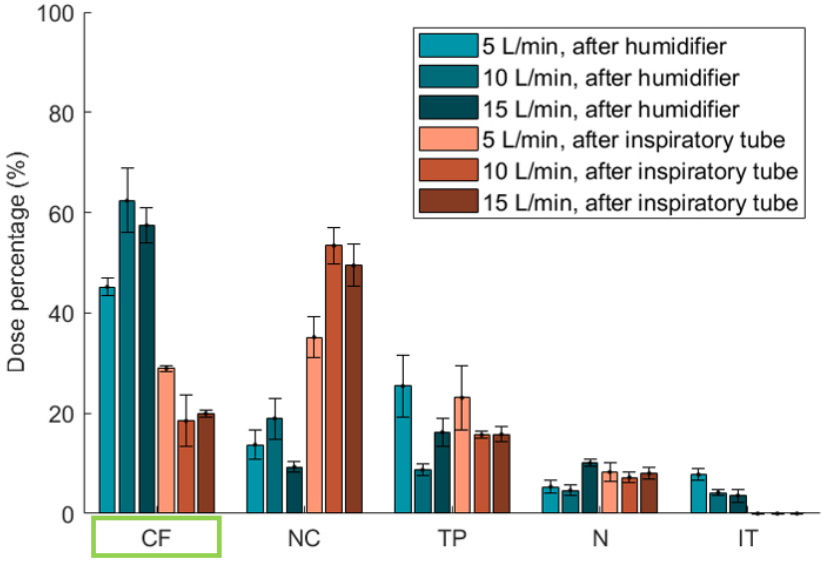

Figure 4: Deposition (mean and standard deviation) in various breathing circuit components for two different nebulizer positions when using the decoupled humidifier. CF: collection filter (delivered dose), NC: nasal cannula, TP: T-piece, N: nebulizer, IT: inspiratory tube.

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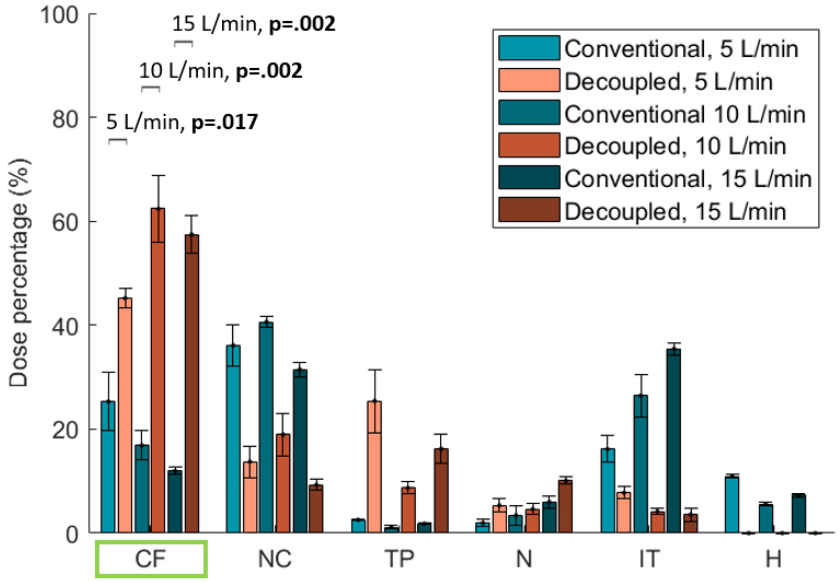

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413x303mm (47 x 47 DPI)

Table 1: Relative humidity (RH) at the end of the inspiratory tube, at the start (immediately before turning on the nebulizer) and at the end of nebulization for the decoupled humidifier setup.

Air flow rate (L/min)	RH at the start of nebulization	RH at the end of nebulization
5	12.5% ± 1.3%	86.4% ± 7.3%
10	6.0% ± 5.5%	53.2% ± 1.7%
15	7.0% ± 5.2%	36.7% ± 6.5%